A. M. A.
ARCHIVES OF
SURGERY

EDITORIAL BOARD

WALTMAN WALTERS, Chairman, Rochester, Minn.

LESTER R. DRAGSTEDT, Chicago

ROBERT ELMAN, St. Louis

ALTON OCHSNER, New Orleans

ARTHUR W. ALLEN, Boston

ALFRED BLALOCK, Baltimore

FRANK HINMAN Jr., San Francisco

G. E. LINDSKOG, New Haven, Conn.

BARNES WOODHALL, Durham, N. C.

JANUARY 1953

VOLUME 66 NUMBER 1

Published Monthly by

AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter July 10, 1925, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $14.00

TABLE OF CONTENTS FIRST PAGE

THE A. M. A. ARCHIVES OF SURGERY is published by the American Medical Association for the advancement of surgery and as a medium of publication for research, clinical observations and experimental work in surgery.

Manuscripts for publication and correspondence relating to the editorial management, to communications, subscriptions, reprints, etc., should be addressed, A. M. A. ARCHIVES OF SURGERY, American Medical Association, 535 North Dearborn Street, Chicago 10.

Articles are accepted for publication on condition that they are contributed solely to the A. M. A. ARCHIVES OF SURGERY. Manuscripts must be typewritten, preferably double spaced, and the original copy should be submitted. Zinc etchings and halftones will be supplied by the Association when the original illustrations warrant reproduction and when their number is not considered excessive.

Footnotes and bibliographies (the latter are used only in exhaustive reviews of the literature) should conform to the style of the *Quarterly Cumulative Index Medicus*. This requires, in the order given: name of author, title of article and name of periodical, with volume, page, month—day of month if the journal appears weekly—and year.

Matter appearing in the A. M. A. ARCHIVES OF SURGERY is covered by copyright, but as a rule no objection will be made to its reproduction, in a reputable medical journal if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the A. M. A. ARCHIVES OF SURGERY or in any of the other publications issued by the Association will not be permitted.

The A. M. A. ARCHIVES OF SURGERY is issued monthly. The annual subscription price (for two volumes) is as follows: domestic, $14.00; Canadian, $14.40; foreign, $15.50, including postage. Current single copies are $1.25, postpaid, except special numbers.

Checks, money orders and drafts should be made payable to the American Medical Association.

OTHER PERIODICAL PUBLICATIONS

of the American Medical Association

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION—Weekly. Covers all the medical sciences and matters of general medical interest. Illustrated. Annual subscription price (three volumes): domestic, $15.00; Canadian, $16.50; foreign, $19.00. Single copies, 45 cents.

A. M. A. ARCHIVES OF INTERNAL MEDICINE—Monthly. Devoted to the publication of advanced original clinical and laboratory investigations in internal medicine. Illustrated. Annual subscription price (two volumes): domestic, 10.00; Canadian, $10.40; foreign, $11.00. Single copies, $1.00.

A. M. A. ARCHIVES OF NEUROLOGY AND PSYCHIATRY—Monthly. A medium for the presentation of original articles on nervous and mental diseases, with abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.50. Single copies, $1.25.

A. M. A. ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY—Monthly. Devoted to advancing the knowledge of and progress in cutaneous diseases and syphilis. Publishes original contributions on these two subjects, transactions of the important dermatological societies, book reviews, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.50. Single copies, $1.25.

A. M. A. AMERICAN JOURNAL OF DISEASES OF CHILDREN—Monthly. Presents pediatrics as a medical science and as a social problem. Includes carefully prepared reviews, based on recent pediatric literature, abstracts from foreign and domestic literature, book reviews, transactions of special societes, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.50. Single copies, $1.25.

A. M. A. ARCHIVES OF OPHTHALMOLOGY—Monthly. Includes original articles on diseases of the eye, annual reviews of special subjects, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.00. Single copies, $1.25.

A. M. A. ARCHIVES OF OTOLARYNGOLOGY—Monthly. A medium for the presentation of original articles on diseases of the ear, nose and throat, with abstracts from foreign and domestic literature, book reviews, transactions of special societies, etc. Illustrated. Annual subscription price (two volumes): domestic, $12.00; Canadian, $12.40; foreign, $13.00. Single copies, $1.25.

A. M. A. ARCHIVES OF PATHOLOGY—Monthly. A periodical devoted to the publication of original articles and general reviews in the field of pathology. Illustrated. Annual subscription price (two volumes): domestic, $8.00; Canadian, $8.40; foreign, $9.00. Single copies, $1.00, except special issues.

A. M. A. ARCHIVES OF INDUSTRIAL HYGIENE AND OCCUPATIONAL MEDICINE—Monthly. Devoted to the advancement of knowledge of the diseases of industry and to the publication of scientific investigation in this field. Illustrated. Annual subscription price (two volumes): domestic, $8.00; Canadian, $8.40; foreign, $9.00, including postage. Single copies, $1.00.

QUARTERLY CUMULATIVE INDEX MEDICUS—A complete subject and author index to the worth while current medical literature of the world. Issued twice a year. Volumes bound for permanent reference. Subscription price, calendar year: domestic, $20.00; Canadian, $22.00; foreign, $22.00.

AMERICAN MEDICAL ASSOCIATION

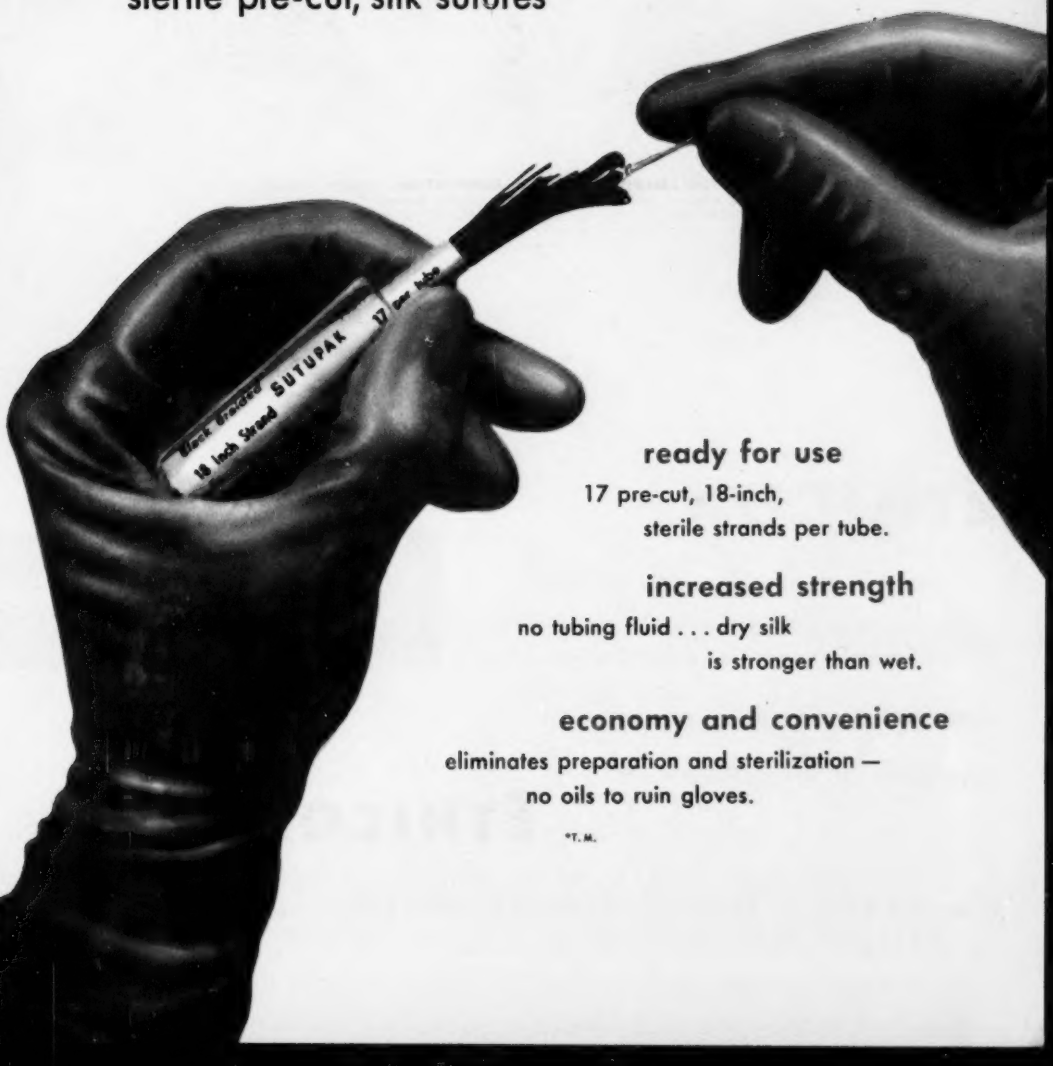
535 North Dearborn Street **CHICAGO 10**

New

ETHICON®

SUTUPAK*

sterile pre-cut, silk sutures



ready for use

17 pre-cut, 18-inch,
sterile strands per tube.

increased strength

no tubing fluid . . . dry silk
is stronger than wet.

economy and convenience

eliminates preparation and sterilization —
no oils to ruin gloves.

*T. M.

Uniform Absorption

ETHICON® *Catgut*

Ethicon Tru-Chromicized catgut is absorbed at a remarkably uniform rate, regardless of suture size.

always specify **ETHICON** *Sutures*

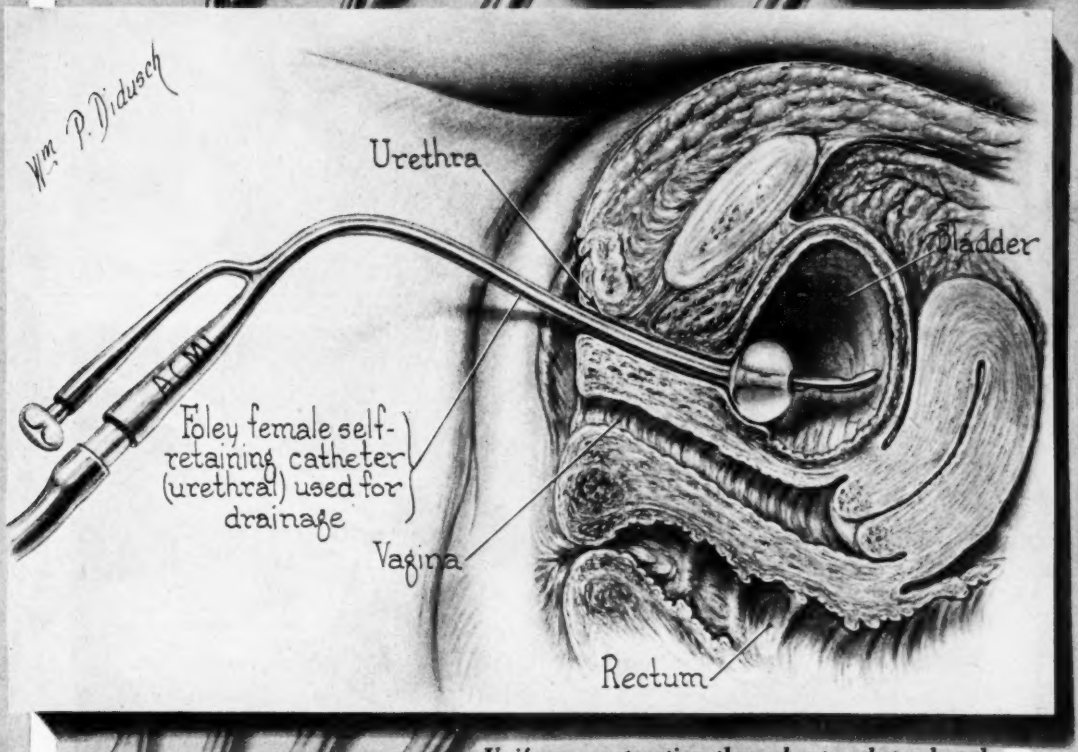
ETHICON SUTURE LABORATORIES INCORPORATED, NEW BRUNSWICK, N.J.

for dependable

HEMOSTATIC BAG CATHETERS

specify

A.C.M.I.



- *Uniform construction throughout catheter length*
- *Correctly marked for size*
- *Large lumen permits maximum drainage*

ESTABLISHED IN 1900 — BY REINHOLD WAPPLER

FREDERICK J. WALLACE, *President*

American Cystoscope Makers, Inc.

1241 LAFAYETTE AVENUE — NEW YORK 59, N. Y.

Only BEAVER
makes replaceable bent blades

BEAVER BENT BLADES permit better technique in deep operations such as arthroplasty, semi-lunar cartilage and laminectomy. Also in hysterectomy, gall bladder and thorax. No. 14 (sharp all around), No. 16 (sharp on one edge only), and No. 18 (sharp on two edges with a safe point). ALL BEAVER BENT BLADES are rigidly tested for strength before leaving the factory — they fit all BEAVER KNIFE HANDLES.

RUDOLPH BEAVER
WALTHAM 54, MASS., U. S. A.

SURGICAL KNIVES BY
Rudolph
Beaver

Resilient, tempered steel polished needles with sharp points and keen cutting edges, securely anchored to specified lengths of Deknatel Moisture and Serum Resistant Surgical Silk.

DEKNATEL

A time-saving suturing combination, streamlined to minimize perforation and trauma. Write for full details. J. A. Deknatel & Son, Inc., Queens Village 8, Long Island, New York.

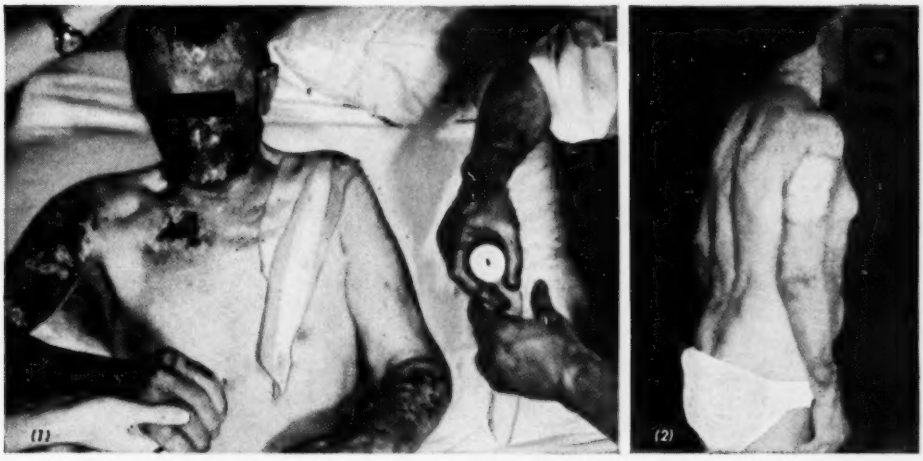
MINIMAL-TRAUMA NEEDLES WITH ATTACHED SUTURES

Surgical Silk, Nylon, Cotton, Readi-Cut Sutures, Name-On Beads.

Reasons for effectiveness of Furacin

A wide antibacterial spectrum, including many gram-negative and gram-positive organisms • Effectiveness in the presence of wound exudates • Lack of cytotoxicity: no interference with healing or phagocytosis • Low incidence of sensitization: less than 5% • Ability to minimize malodor of infected lesions • Stability.

Furacin® preparations contain Furacin 0.2% brand of nitrofurazone N.N.R. in water-miscible vehicles which dissolve in exudates.



IN SEVERE BURNS . . .

A 68 year old patient suffered third degree burns of face, arms and torso. See illustration (1) above. 16 days later fine-mesh gauze, *impregnated with Furacin Soluble Dressing,* was applied next to the burned surface —and covered with wet pressure dressings. Dressings were changed daily. Illustration (2) shows patient, after skin grafting, 6 months later.

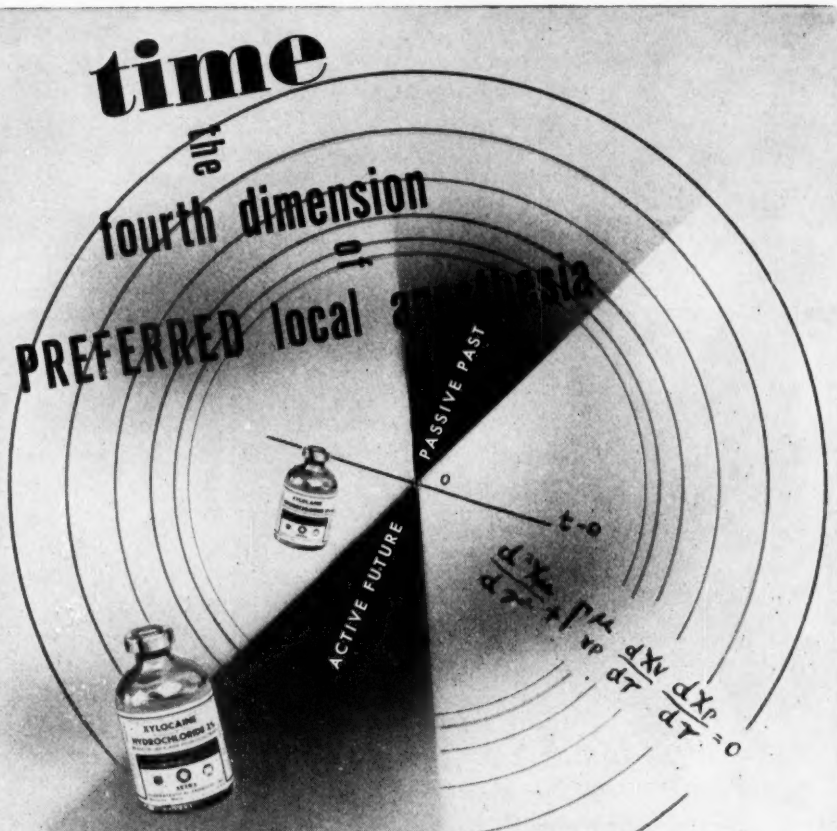
Literature on request

ACCEPTED
COUNCIL ON PHARMACY AND CHEMISTRY
AMA MEDICAL SERVICES
FURACIN†
SOLUBLE DRESSING
N. N. R.
†(BRAND OF NITROFURAZONE)
CONTAINS 0.2% NITROFURAZONE N. N. R. IN A WATER SOLUBLE BASE
CAUTION: TO BE DISPENSED ONLY BY OR ON THE PRESCRIPTION OF A PHYSICIAN.
WARNING: THIS DRUG MAY CAUSE SENSITIZATION. IF THIS OCCURS, ITS USE SHOULD BE DISCONTINUED.
LITERATURE AVAILABLE TO PHYSICIANS ON REQUEST
AN ANTIBACTERIAL PREPARATION FOR TOPICAL APPLICATION
E. A. T. O. N. Inc.
NORWICH, NEW YORK
ONE POUND AVOIR
The NITROFURANS
A unique class of antimicrobials

E. A. T. O. N. LABORATORIES Inc.
NORWICH, NEW YORK

FURACIN SOLUBLE DRESSING • FURACIN SOLUTION • FURACIN ANHYDROUS EAR SOLUTION

time
the fourth dimension in PREFERRED local anesthesia



QUICK-ACTING

Stocked by leading wholesale druggists and surgical supply houses as a ½%, 1% or 2% solution without Epinephrine and with Epinephrine 1:100,000. 2% solution is also supplied with Epinephrine 1:50,000. All solutions dispensed in 50cc. and 20cc. multiple dose vials, packed 5x50cc. or 5x20cc. to a carton.

Xylocaine® Hydrochloride (Astra) merits special consideration by the busy anesthesiologist and surgeon. Profound in depth and extensive in spread, its well-tolerated effect is more significantly measured by the time saved through its remarkably fast action, by which so much normally wasted "waiting time" is converted to productive "working time".

XYLOCAINE® HCL

Pronounced Xī lo'cain

(Brand of lidocaine hydrochloride*)

AN AQUEOUS SOLUTION

A 4th dimensional approach to preferred local anesthesia

Bibliography available on request

ASTRA PHARMACEUTICAL PRODUCTS, INC. WORCESTER, MASS. U.S.A.

*U.S. Patent No. 2,441,498

A. M. A.
ARCHIVES OF SURGERY

VOLUME 66 JANUARY 1953 NUMBER 1

COPYRIGHT, 1953, BY THE AMERICAN MEDICAL ASSOCIATION

OBSERVATIONS ON EFFECT OF METHANTHELINE (BANTHINE®) BROMIDE IN UROLOGICAL DISTURBANCES

JACK LAPIDES, M.D.
AND
AUSTIN I. DODSON Jr., M.D.
ANN ARBOR, MICH.

RECENTLY, we gave a preliminary report [1] concerning the effects of methantheline (banthine®) bromide on the neuromuscular mechanisms of the urinary tract and indicated some useful therapeutic applications of this compound. It was also noted that further uses for methantheline bromide in urological disturbances were being investigated and would be reported when experimental data permitted definite conclusions.

In the present paper the action of methantheline bromide in patients with a variety of clinical disturbances will be discussed. These entities and the results of treatment will be described separately.

Methantheline bromide is a quaternary ammonium derivative,[2] β-diethylaminoethyl-9-xanthenecarboxylate methobromide, which has been found to block transmission of nerve impulses through autonomic ganglia as well as at postganglionic cholinergic nerve endings.[3] The drug is effective both orally and parenterally and has demonstrated no harmful side-effects.[1]

I. NEUROGENIC ENURESIS

Before discussing the effect of methantheline bromide in neurogenic enuresis, it would be well to differentiate this form of incontinence from other types. Stress incontinence is encountered most frequently in females and is an involuntary voiding of urine produced by coughing, sneezing, lifting, etc. Overflow or paradoxical incontinence occurs primarily in males and is characterized by a constant involuntary

---

Dr. Lapides is a George L. McKesson Fellow.

Banthine® was supplied by G. D. Searle & Company.

From the Department of Surgery, University of Michigan Medical School.

This study was supported by a research grant from G. D. Searle & Company.

Read before the Section on Urology at the One Hundred and First Annual Session of the American Medical Association, Chicago, June 11, 1952.

1. Lapides, J., and Dodson, A. I., Jr.: Preliminary Report: A Study of The Effects of Banthine® on the Human Bladder, J. Urol., to be published.

2. Cusic, J. W., and Robinson, R. A.: Autonomic Ganglion Blocking Agents—Quaternaries of Basic Esters of Some Polynuclear Carbolic Acids and Tropic Acid, read before the Medicinal Division of the American Chemical Society Meeting, Philadelphia, April 9-13, 1950.

3. Hambourger, W. E.; Cook, D. L.; Winbury, M. M., and Freese, H. B.: Pharmacology of β-Diethylaminoethyl Xanthine-9-Carboxylate Methobromide (Banthine) and Chloride, J. Pharmacol. & Exper. Therap. **99**:245-254, 1950.

dribbling of urine; this condition is due to urinary retention with overflow. Another form of dribbling incontinence is seen in patients with injury to both the internal and the external urinary sphincters. Neurogenic enuresis is a type of urinary incontinence which is intermittent in character and is due to a defect in cortical control; it is not a functional disorder. Patients with a mild defect in cortical control may not be incontinent but will exhibit increased frequency of urination, nocturia, urgency, and precipitate micturition.

The type of bladder observed in patients with defective cortical control has been designated as the "uninhibited neurogenic bladder." [4] This type of bladder is often seen in patients with multiple sclerosis, brain tumors, injuries and tumors of the spinal cord, syphilitic dementia paralytica, cerebral palsy, postchordotomy, and after cerebrovascular accidents. In these conditions there are lesions involving either the upper motor neurones or the cortical regulating tracts which are concerned with the voluntary control of micturition.

Not infrequently one encounters patients with symptoms of urgency, increased frequency of urination, and precipitate micturition, as well as nocturnal enuresis, who exhibit no other evidences of neurologic disturbance. In these persons, defective voluntary control of urination is believed to be due to incomplete development of cerebral integration, a situation which is present universally in the infant and in the young child. In normal persons, complete integration with voluntary control it attained at the age of 3 to 5 years. In adults with the congenital type of neurogenic enuresis, complete cerebral integration never develops.

In order to make a positive diagnosis of uninhibited neurogenic bladder it is necessary to perform a cystometric examination,[5] for not all patients with increased frequency of urination, precipitate micturition, and bed-wetting have neurogenic enuresis; in fact, many patients who exhibit these symptoms will be found by complete examination to be suffering from psychogenic disorders. It is of importance therefore to differentiate between neurogenic and psychogenic enuresis, for, as will be shown, methantheline bromide is effective in the control of neurogenic enuresis but not of psychogenic enuresis.

Figure 1 *A* is the cystometrogram of the typical uninhibited neurogenic bladder found in neurogenic enuresis, while Figure 1 *B* is the cystometrogram of a normal bladder. Note that the normal bladder exhibits a smooth curve while it is being filled with fluid and that no voiding contractions occur. The uninhibited bladder, however, demonstrates several sharp contractions with a final uncontrolled voiding contraction. The neurogenic enuretic patient has normal bladder sensation, can usually initiate micturition at will, and empties the bladder completely on voiding. However, these patients have varying degrees of difficulty inhibiting micturition. When the urge to void occurs, they are acutely uncomfortable and many of them are unable to prevent the immediate onset of urination.

As has been stated previously, the symptoms of the neurogenic enuretic are due to a defect in cerebral integration or to lesions of the cortical regulating tracts which result in the failure of proper inhibition of urination. The local reflex arc and spinal pathways concerned with micturition are illustrated in Figure 2. In the normal person, as the bladder fills with urine and is distended, stretch receptors in the

4. Nesbit, R. M.: Fundamentals of Urology, Ann Arbor, Mich., J. W. Edwards, 1948.

5. Nesbit, R. M., and Lapides, J.: Tonus of the Bladder During Spinal "Shock," Arch. Surg. **56**:139-144, 1948.

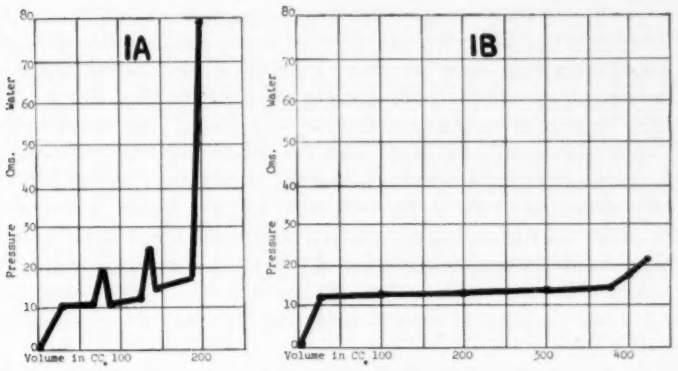


Fig. 1.—*A*, cystometrogram of uninhibited neurogenic bladder. *B*, cystometrogram of normal bladder.

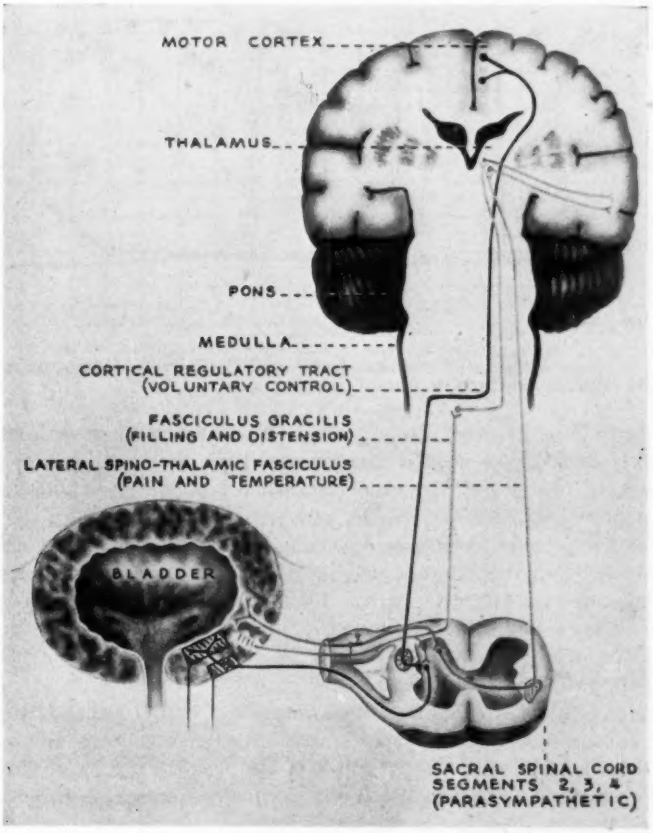


Fig. 2.—Local reflex arc and spinal pathways concerned with micturition. Motor impulses blocked at ganglionic synapse and postganglionic endings by use of methantheline bromide.

bladder wall are stimulated to give rise to sensory impulses which are conducted along sensory fibers in the pelvic nerve to the spinal cord. In the spinal cord the sensory impulses impinge upon the motor neurones of the bladder (located at the level of the second, third, and fourth sacral spinal segments) and also are conducted to the higher centers along the ascending sensory tracts. The motor neurones do not respond to the sensory impulses until the person voluntarily desires to void. The cortical regulating tract, which has endings around the lower motor neurones, prevents the discharge of the motor neurones until the higher center releases its inhibitory effect. In the neurogenic enuretic patient the lower motor neurones are not effectively inhibited because of a lesion of the cortical regulating tracts, and, thus, as the bladder is moderately distended, sensory impulses impinge upon the motor neurones and activate some of them to send motor impulses to the bladder, causing its contraction.

Since the motor pathway to the bladder is over parasympathetic fibers in the pelvic nerve, it would be expected that methantheline bromide, with its properties of blocking motor impulses at the ganglia as well as at postganglionic cholinergic

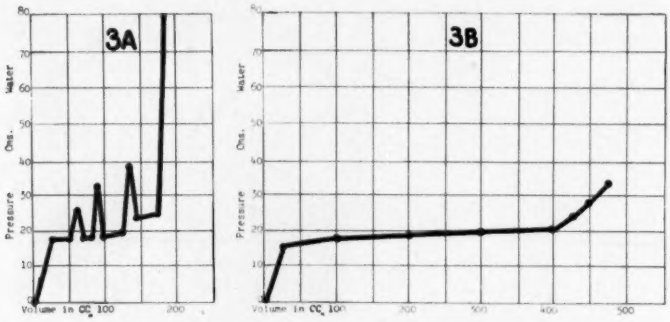


Fig. 3.—*A*, cystometrogram of uninhibited neurogenic bladder. *B*, cystometrogram of same bladder after methantheline bromide therapy (large doses).

nerve endings (Fig. 2), would have some effect on micturition in both normal and abnormal bladders. Experimental observations [1] have disclosed that in normal persons a dose of 150 to 200 mg. of methantheline bromide given intravenously is capable of producing complete bladder paralysis with acute urinary retention for a period of 3 to 5 hours. The same dose of methantheline bromide administered to a patient with neurogenic enuresis will abolish all uninhibited voiding contractions and increase apparent bladder capacity. Figure 3 *A* illustrates the cystometrogram of an uninhibited neurogenic bladder, and Figure 3 *B* depicts the same bladder after methantheline bromide administration; note the disappearance of all voiding contractions and the increase in apparent bladder capacity.

Moderate oral doses of methantheline bromide (50 to 150 mg.) four times a day have been administered to patients with neurogenic enuresis and to patients with psychogenic enuresis. The patients with neurogenic enuresis showed remarkable improvement in symptoms, while the psychogenic enuretics demonstrated no relief of symptoms. Figure 4 *A* illustrates the cystometrogram of an uninhibited neurogenic bladder, taken prior to methantheline bromide administration, and Figure 4 *B*, the cystometrogram during therapy with moderate doses of methantheline

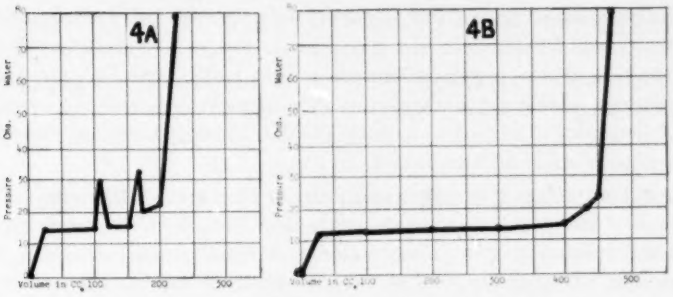


Fig. 4.—*A*, cystometrogram of uninhibited neurogenic bladder. *B*, cystometrogram of same bladder after methantheline bromide therapy (moderate doses).

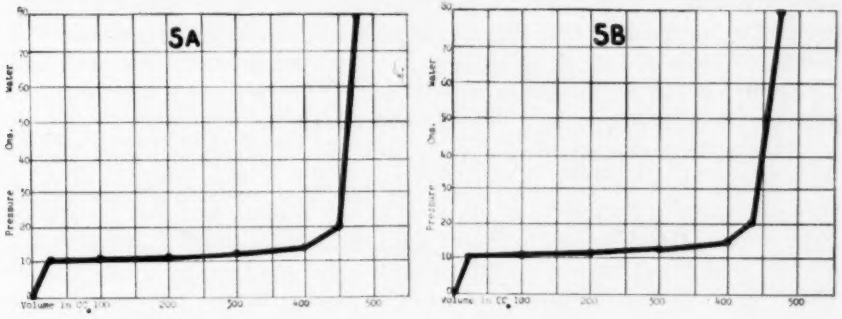


Fig. 5.—*A*, cystometrogram of bladder of psychogenic enuretic patient. *B*, cystometrogram of same bladder after therapy with methantheline bromide (moderate doses).

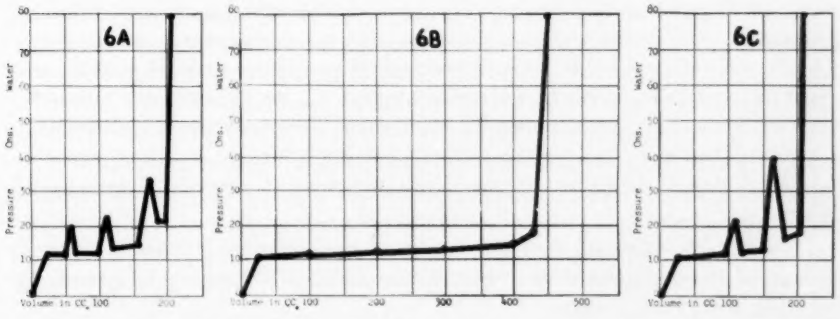


Fig. 6.—*A*, cystometrogram of bladder of neurogenic enuretic patient before methantheline bromide therapy. *B*, cystometrogram of same bladder during methantheline bromide therapy. *C*, cystometrogram of same bladder three days after cessation of methantheline bromide therapy.

bromide. It will be observed that the involuntary contractions have been abolished and that the bladder capacity has been increased. The patient was able to void at will, with no residual urine. The frequency of urination had decreased to within normal limits, and incontinence had disappeared. Figure 5 *A* illustrates the normal cystometrogram of a psychogenic enuretic patient and Figure 5 *B*, the unchanged cystometrogram during methantheline bromide therapy. This patient's symptoms of increased frequency of urination, urgency and incontinence were not altered during methantheline bromide administration.

Some of the patients with neurogenic enuresis were given methantheline bromide orally for five days, and then therapy was discontinued. Cystometrograms were obtained before administration of methantheline bromide was begun, during therapy, and three days following cessation of therapy. Figure 6 *A* is the pre-methantheline-bromide cystometrogram; Figure 6 *B* is the cystometrogram during methantheline bromide therapy; and Figure 6 *C* is the post-methantheline-bromide cystometrogram. Observe the abolition of the uninhibited contractions and the increase in bladder capacity during methantheline bromide therapy and the recurrence of the involuntary contractions following discontinuance of methantheline bromide. The patient's symptoms were in accord with the cystometrograms in that symptoms disappeared during administration of methantheline bromide and reappeared when methantheline bromide therapy was discontinued.

To date, 30 neurogenic enuretic persons with the uninhibited neurogenic bladder have been given methantheline bromide orally in a dose of 50 to 150 mg. four times a day for varying periods up to 10 months. All patients have had remarkable improvement in symptoms. No patient with increased frequency of urination and enuresis who demonstrates a normal cystometrogram was benefited by administration of methantheline bromide. Methantheline bromide therapy does not help the psychogenic enuretic patient.

II. VISCERAL PAIN

Intravenous injections of methantheline bromide in a dose of 100 to 200 mg. were administered to the following patients: 7 patients with bladder pain following cystoscopy, 10 patients with bladder pain following transurethral prostatectomy, 15 patients with renal colic following retrograde pyelography, and 8 patients with renal and ureteral colic due to a ureteral calculus. All the patients were relieved of pain within 3 to 10 minutes after the intravenous administration of methantheline bromide. The relief of pain in these cases, particularly ureteral colic, has been spectacular. Some of the patients required repeated doses at intervals of three to five hours.

It might be mentioned that each 50 mg. of methantheline bromide is dissolved in 5 ml. of sterile water and that the total dose of 100 to 200 mg. can be given intravenously within one minute.

The exact mechanism or action by which methantheline bromide relieves visceral pain is not known at present. Experiments [1] indicate that this drug does not block sensory nerve transmission of impulses. Cystometric studies before and after relief of pain by methantheline bromide in six patients with spastic painful bladders do not demonstrate relaxation of the detrusor urinae coincidental with pain dissolution.

On the basis of previous research in the field of pain,[6] one might cautiously propose the possibility that methantheline bromide relieves some types of visceral pain by increasing the blood supply (through its action on the autonomic ganglia) to the affected organ.

Although all our patients with visceral pain responded readily to methantheline bromide therapy, it will be necessary to treat many more before the drug can be evaluated accurately.

III. INTERSTITIAL CYSTITIS

Shortly after methantheline bromide became available for general use, an informal preliminary report by Ormond indicated that this drug might be useful in the treatment of Hunner's ulcer. Accordingly, six patients with interstitial cystitis were treated with moderate doses of methantheline bromide over a period of one to three months. Several patients appeared to have remarkable improvement in symptoms shortly after methantheline bromide therapy was instituted, but the increased frequency of urination and pain soon returned. Prolonged observation revealed that none of the patients with interstitial cystitis obtained lasting relief from continued therapy with methantheline bromide.

IV. SMALL CAPACITY BLADDERS

Not infrequently the urologist finds it desirable to enlarge a small capacity bladder in order to perform an operative procedure (e. g., transurethral prostatectomy or litholapaxy) or to improve urinary vesical function. It has been shown [7] that hydrostatic distention of the bladder over a period of time will often result in an increase in bladder capacity. This can be accomplished usually either by tidal irrigation or by elevating the drainage-tube system above the level of the bladder.

There are certain types of small capacity bladders, however, which resist this method of treatment and tend to evacuate themselves either through or around an inlying catheter as soon as a minimal amount of fluid collects in the bladder. In one type, the reflex neurogenic bladder of the paraplegic, the voiding contractions of the detrusor urinae are uncontrolled because higher center regulation has been abolished by a lesion of the spinal cord.

Another type of small capacity bladder, often seen clinically, is that which sometimes follows decompression of a distended bladder in prostatism or postoperative retention. This type of spastic bladder resents catheter drainage, and any attempt at filling the bladder results in pain and immediate evacuation.

Methantheline bromide has been found to be an effective aid in enlarging small capacity bladders of these types. As has been indicated, methantheline bromide can be given in large enough doses to block the motor impulses to the bladder completely and thus prevent either voluntary or involuntary expulsion when it is distended. When the bladder distends under these conditions, it is found no longer to be painful.

6. Lewis, T.: Pain, New York, The Macmillan Company, 1942. Coller, F. A.; Campbell, K. N.; Berry, R. E.; Sutler, M. R.; Lyons, R. H., and Moe, G. K.: Tetra-Ethyl-Ammonium as an Adjunct in the Treatment of Peripheral Vascular Disease and Other Painful States, Ann. Surg. **125**:729-755, 1947. Sborov, V. M., and Bluemle, L. V.: Tetraethylammonium Chloride in Pain, U. S. Armed Forces M. J. **1**:546-549, 1950.

7. Lapides, J.: Some Observations on Normal and Abnormal Bladder Physiology, J. Urol., to be published.

Large doses of methantheline bromide administered orally and parenterally in conjunction with bladder distention have been used to increase the capacity in 10 spastic reflex neurogenic bladders and in 12 spastic bladders resulting from decompression. In these reflex neurogenic bladders, increased capacity could not be accomplished in a practical way without use of methantheline bromide. (To be sure, the same results could be obtained by spinal anesthesia, but this method of blocking motor impulses is not a practical therapeutic device.) This was demonstrated experimentally in the following manner: A cystometrogram was first obtained on the patient to be tested. Then the Y-tube of the drainage system was elevated for a period of one week. At the end of that time another cystometrogram was obtained. After the second study, the patient was given methantheline bromide orally, 200 mg. every four hours. The Y-tube was kept in its original position. At the end of one week of methantheline bromide therapy, cystometrography was repeated. Figure 7 *A* demonstrates the cystometrogram of a spastic reflex neurogenic bladder before distention without methantheline bromide and 7 *B*, the cysto-

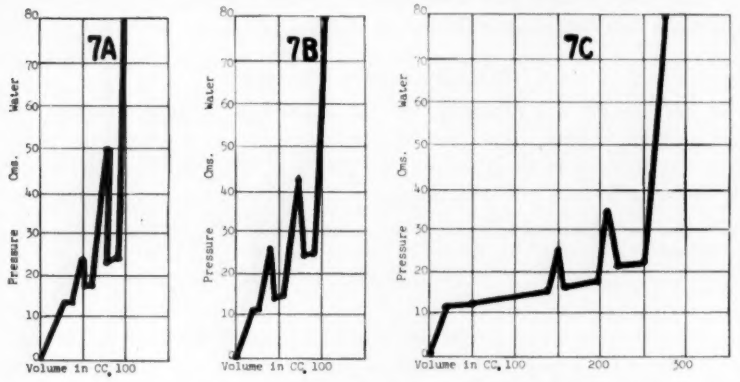


Fig. 7.—*A*, cystometrogram of spastic reflex neurogenic bladder of paraplegic. *B*, cystometrogram of same bladder after one week of hydrostatic distention. *C*, cystometrogram of same bladder after another week of hydrostatic distention and methantheline bromide therapy.

metrogram after a week's distention without methantheline bromide. Observe that there is no difference in the cystometrograms. In Figure 7 *C*, which is the cystometrogram obtained after one week of methantheline bromide therapy and distention, note the definite enlargement in bladder capacity.

Since accurate control observations were not done in the study on the spastic bladders resulting from decompression, a scientifically valid statement cannot be made regarding the effectiveness of methantheline bromide in this type of bladder. However, the patients so treated were relieved of strangury and, instead of voiding around their catheters, were observed to have increased capacity and comfort.

V. PRECAUTIONS

One should not administer large doses of methantheline bromide to patients with glaucoma because mydriasis always occurs.

Patients without inlying catheter drainage of the bladder should always be instructed to empty their bladders before large doses of methantheline bromide are

given, since the bladder will be paralyzed for a period of four to six hours following administration. One should be aware of the fact that moderate doses of methantheline bromide may precipitate acute urinary retention in patients suffering from prostatism. Care should be taken in using methantheline bromide in patients with severe cardiac disease, since large doses of this drug may produce tachycardia.

CONCLUSIONS

1. Methantheline (banthine®) bromide is effective in the palliative treatment of neurogenic enuresis but not of psychogenic enuresis.

2. Renal and ureteral colic, as well as bladder pain, can be abolished abruptly by intravenous administration of methantheline bromide.

3. Interstitial cystitis is not relieved by long-term therapy with methantheline bromide.

4. Methantheline bromide augments the effectiveness of hydrostatic distention in enlarging the capacity of certain types of spastic bladders.

ABSTRACT OF DISCUSSION

DR. WILLIAM J. BAKER, Chicago: My remarks will be confined to the presentation of Drs. Lapides and Dodson. They have presented an interesting, instructive and scholarly study of methantheline (banthine®) bromide. Their use of this drug to differentiate neurogenic enuresis from psychogenic enuresis should be a great aid to all of us. Too many people are told that they have a nervous bladder, without proper differentiation. Methantheline bromide should enable us to separate the behavior problems from true neurogenic problems.

However, it should be stated that some of the patients with neurogenic enuresis are completely relieved by a transurethral revision of the unsuspected or unrecognized contracture of the vesical neck.

The use of methantheline bromide is preferable for all bedfast patients with an uninhibited neurogenic bladder.

It is a fact that the intravenous use of methantheline bromide will alleviate pain which follows urological instrumentation. Methantheline bromide administered intravenously also controls the pain of renal and ureteral colic. It should be stated, also, that the required amount of methantheline bromide to relieve the pain of the above conditions will, in many instances, produce acute urinary retention. Then confusion rules. The control of pain in these conditions by hypodermic opiates or by rectal suppositories of anodynes still has great merit.

There is no doubt that this drug will be used more and more in urological work. It is believed that it should always be used with caution because it is a paralyzing drug.

We are grateful to Drs. Lapides and Dodson for presenting their work. They have informed and stimulated all of us. It is hoped that they will continue their observations and make a further report.

GASTROINTESTINAL HEMORRHAGE FROM BENIGN TUMORS OF THE DUODENUM

JOHN D. BRIGGS, M.D.
AND
JOHN F. ROBERTS, M.D.
LOS ANGELES

SEVERAL investigators [1] have emphasized that even though benign tumors of the small bowel occur rarely, they should be considered in differential diagnosis of unexplained bleeding from the gastrointestinal tract. Rankin and Newell [2] have noted that bleeding occurred from benign tumors of the duodenum more frequently than from similar lesions located elsewhere in the small bowel. A majority of these neoplasms are asymptomatic and are discovered either at operation or autopsy. However, hemorrhage is the commonest symptom associated with them and may be the only one.

Diagnosis of bleeding duodenal neoplasms is often difficult to make. There is no clinical syndrome that is peculiar to these lesions, and roentgenographic studies may be of no aid. Because of the retroperitoneal location of the duodenum, palpation and transillumination of the region are difficult. Small duodenal tumors are thus more easily overlooked than are those in the jejunum and ileum. We wish to describe our experience with three patients in whom benign duodenal neoplasms were found. Two of them had massive, and the third, moderate, gastrointestinal hemorrhage as their presenting symptom.

REPORT OF CASES

CASE 1.—A. J. T., a 58-year-old white man, was first admitted to Wadsworth Hospital, Veterans Administration Center, on June 24, 1949, complaining of anemia which had been recurring since 1945. The initial onset of anemia was made manifest by weakness, fatigue, and a mild exertional dyspnea. The cause of the anemia could not be determined. Repeated roentgenographic studies of the upper and lower gastrointestinal tract were normal. He was treated with iron, liver, and whole blood transfusions, but the anemia recurred with such severity that he required blood transfusions about twice a year. From the onset of the anemia, in 1945, to the time of admission to Wadsworth Hospital, he had received approximately 40 blood transfusions.

From the Surgical Service, Wadsworth Hospital, Veterans Administration Center, and the Department of Surgery, University of California School of Medicine at Los Angeles.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. Allison, T. D., and Babcock, J. R.: Lipoma of the Duodenum Causing Melena, Ann. Surg. **127**:754-756 (April) 1948. Rankin, F. W., and Grimes, A. E.: Small Bowel Tumors with Special Reference to Melena, South. Surgeon **6**:280-287 (Aug.) 1937. Segal, H. L.; Scott, W. J., and Watson, J. S.: Lesions of the Small Intestine Producing Massive Hemorrhage, J. A. M. A. **129**:116-120 (Sept. 8) 1945. Smith, L. A.; Good, C. A., and Gray, H. K.: Tumor of the Small Intestine as the Cause of Recurrent Melena: Report of 2 Cases, Proc. Staff Meet., Mayo Clin. **19**:117-122 (Mar. 8) 1944.

2. Rankin, F. W., and Newell, C. E.: Benign Tumors of the Small Intestine, Surg., Gynec. & Obst. **57**:501-507 (Oct.) 1933.

He gave no history of weight loss, abdominal pain, gastric distress, dyspepsia, nausea, vomiting, anorexia, or diarrhea. His past history was noncontributory.

On physical examination the patient was found to be a pale obese man weighing 201 lb. (91 kg.) who was 68 in. (172 cm.) tall. His blood pressure was 185 systolic and 80 diastolic. The spleen and liver were both palpable for 2 to 3 cm. beneath the respective costal margins. There was brown stool in the rectum.

The red blood cell count was 2,560,000, with a hemoglobin level of 8.5 gm. per 100 cc. The white blood cell count was 4,000 on admission, with a normal differential distribution and a normal number of platelets. Examinations of stools reapeatedly revealed occult blood. No free

Fig. 1 (Case 1).—Adenoma of Brunner's glands; × 350.

hydrochloric acid was found in the stomach following the administration of histamine. Upper gastroinestinal x-ray studies showed only slight scarring of the duodenal cap. Needle biopsy of the liver and aspiration of the bone marrow gave normal results.

The patient was operated upon on Nov. 18, 1949, and a thorough exploration of the entire gastrointestinal tract failed to reveal any cause for the hemorrhage. The stomach and duodenum were not opened. A splenectomy was done because of the enlargement of the spleen and liver and because of the mild leucopenia. The spleen was found to weigh 300 gm. but was not otherwise abnormal.

His postoperative course was uneventful, and he was discharged from the hospital on Dec. 19, 1949.

He was readmitted to the hospital on March 23, 1950, with a history of having been in good health until two weeks previously, at which time he again began to have tarry stools, followed in a few days by weakness, exertional dyspnea, and pallor. At no time did he have any abnormal gastrointestinal symptoms other than the tarry stools. Physical examination on this admission gave essentially unchanged results, except that tarry stool was found in the rectum. The liver was still enlarged.

The red blood cell count was 1,220,000, with a hemoglobin level of 4.24 gm. per 100 cc. The white blood cell count was 12,800, with a normal differential distribution and platelet count.

Fig. 2 (Case 2).—Adenoma of intestinal glands; × 90.

Roentgenologic studies of the upper gastrointestinal tract at this time revealed a lesion which appeared to be polypoid in nature, in the first portion of the duodenum.

Reexploration was performed on May 15, 1950, at which time a polyp measuring 7.5 by 1.5 cm. was found attached to the wall of the duodenum by a narrow pedicle just distal to the pylorus. The polyp was removed through a longitudinal duodenotomy, which was then sutured transversely. The postoperative course was normal.

On microscopic examination the polyp was found to consist of Brunner's glands. The overlying mucosa was normal, except for evidence of mild chronic inflammation.

This patient was seen two years after the removal of the polyp. He had had no further bleeding or other symptoms referable to his gastrointestinal tract.

CASE 2.—G. J. H., a 39-year-old white man, was admitted to Wadsworth Hospital on April 4, 1951, because of severe hematemesis and melena of 24 hours' duration. The day before admission he had passed four large tarry stools, and on the day of admission he had vomited coffee-ground-like material on three occasions. He had weakness, faintness, and exertional dyspnea following the onset of the hemorrhage. There was no history of abdominal pain, food intolerance, or other gastrointestinal complaints.

This patient had been admitted to Wadsworth Hospital on five previous occasions, the first time being in December, 1945, and the fifth time in March, 1949. The presenting complaints on each of these admissions were similar to the above, i. e., hematemesis and melena. On each

Fig. 3 (Case 2).—Adenoma of intestinal glands; × 350.

previous occasion upper and lower gastrointestinal roentgenographic studies had been made, which revealed no abnormal findings. On each admission he had been treated with whole blood transfusions and had been subsequently discharged without a definite diagnosis having been made. His past history was otherwise noncontributory.

Physical examination showed the blood pressure to be 72 systolic and 40 diastolic and the pulse rate 120. He appeared pale and somewhat listless. There was no tenderness of the abdomen, and no mass or rigidity could be felt. Tarry stool was present in the rectum.

The red blood cell count was 1,820,000, with hemoglobin 6.1 gm. per 100 cc., and the hematocrit level was 15.5. The white blood cell count was 16,800, with 75% polymorphonuclear leucocytes and a normal platelet count. Urinalysis gave normal results.

During the first 24 hours following admission he was given 4,000 cc. of citrated whole blood. He continued to bleed severely, as evidenced by the frequent occurrence of dark bloody stools and occasional emesis of dark material. On the second day of hospitalization he was given 3,500 cc. of whole blood. He subsequently bled very little; consequently, further roentgenographic studies of the upper and lower gastrointestinal tract were made, and they, too, were of no aid in indicating the source of the hemorrhage.

Surgical exploration was performed on April 18. The entire stomach and the small and large bowel were carefully examined by palpation and transillumination, but no abnormalities were found. A duodenotomy was done and the lumen palpated. A large sessile polyp was found on the posterior wall at the beginning of the third portion of the duodenum. Even after the polyp had been located, it could not be palpated through the duodenal wall. A second opening was made in the duodenum and the polyp excised. A frozen section showed it to be benign. The two duodenotomy openings were then closed.

The postoperative course was uneventful, and the patient was discharged from the hospital on the 15th postoperative day.

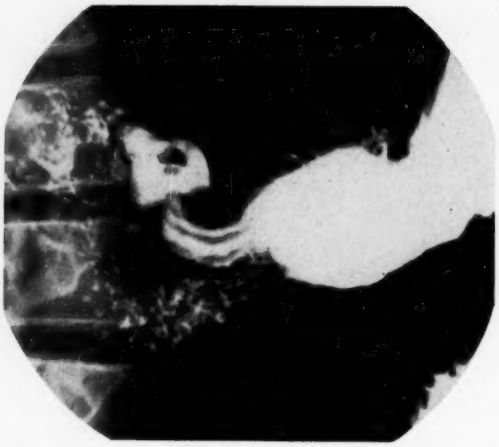


Fig. 4 (Case 3).—Barium study of stomach and duodenum, showing polyp in the duodenal cap.

The polypoid mass of tissue measured 3 by 3 by 1.5 cm. The surface was finely granular and had a tan color. By microscopic examination it was found to be an adenoma composed of intestinal glands.

The patient was seen one year after the operation. During the interim he had had no further bleeding and no complaints referable to his gastrointestinal tract.

CASE 3.—A. L., a 54-year-old white man, was first admitted to Wadsworth Hospital on June 21, 1951, at which time he presented a history of epigastric distress of seven years' duration and intermittent tarry stools of two months' duration. The epigastric pain usually occurred shortly after meals and radiated to the right side of his back. The pain was partially relieved by antacids, and his illness had been diagnosed by his private physician as peptic ulcer. During the two months prior to admission he had noticed on several occasions that his stool had been black. He had not vomited.

Physical examination was entirely within normal limits, except for a moderate obesity and a reducible right inguinal hernia.

The red blood cell count was 4,450,000 and the hemoglobin 15.5 gm. per 100 cc. Multiple radiolucent biliary calculi were found by a gall-bladder dye series. X-ray studies of the upper gastrointestinal tract revealed a radiolucent area which was interpreted as being due to a duodenal polyp in the duodenal cap. The study otherwise revealed a normal condition.

The patient was operated upon June 26, 1951. The gall bladder was found filled with many small calculi and was removed. A small firm nodule could be palpated within the first portion of the duodenum; consequently, a longitudinal incision was made just distal to the pylorus. A polyp about 1 cm. in diameter was found attached to a narrow pedicle, which was clamped, divided, and ligated. The duodenotomy opening was closed transversely.

The polyp was tan-colored and the cut section appeared uniform. Microscopic examination showed it to consist entirely of Brunner's glands covered with normal duodenal mucosa.

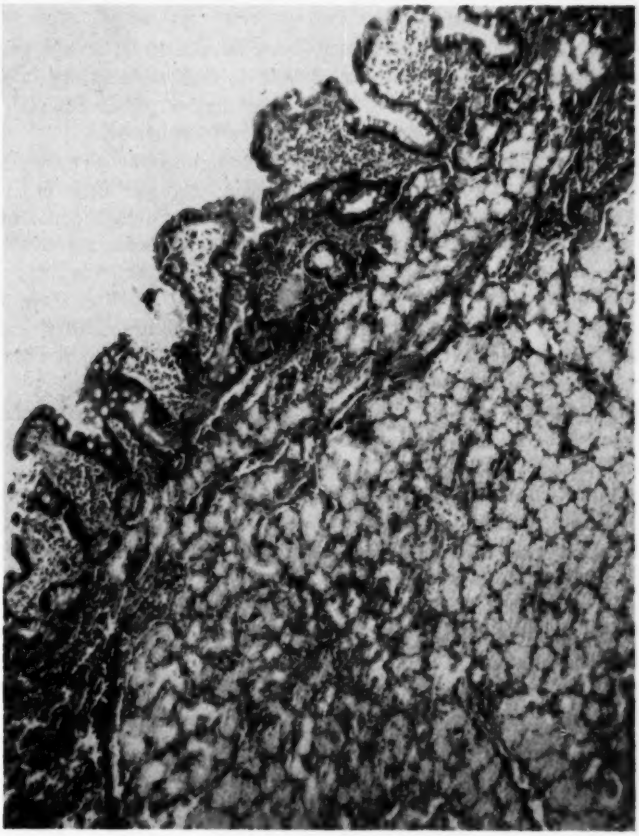


Fig. 5 (Case 3).—Adenoma of Brunner's glands. Tumor lies under normal duodenal mucosa and extends through muscularis mucosae; × 90.

The postoperative course was normal, and the patient was discharged on the 13th postoperative day. He was seen 11 months after removal of the polyp and stated that during the intervening time he had had no further gastrointestinal bleeding.

COMMENT

Benign tumors of the duodenum are uncommon. King,[3] in 1917 reviewed the literature of benign lesions of the intestinal tract and only 5 in a total of 119 of these

3. King, E. L.: Benign Tumors of the Intestines with Special Reference to Fibroma: Report of a Case, Surg., Gynec. & Obst. **25**:54-71 (July) 1917.

lesions were located in the duodenum. In 1928 Ross Golden [4] found only 17 cases of benign duodenal tumor which had been reported to that date and added 2 of his own. Raiford [5] found 21 duodenal tumors, 13 of which were benign, in a series of 11,500 autopsies and 45,000 surgical specimens at The Johns Hopkins Hospital. Weber and Kirklin,[6] in a review of the records of the Mayo Clinic from 1907 to 1939, were able to find 41 instances of benign neoplasm of the small intestine, 17 of which were located in the duodenum. In the same series there were 108 cases of malignant small intestinal tumors.

Although benign duodenal tumors are found in patients of all age groups, they tend to occur in younger patients oftener than do malignant lesions of the bowel. In the series of Rankin and Newell,[2] the average age of patients having duodenal tumors was 41.6 years. There was no predilection to either sex.

Two of the several theories of the origin of benign duodenal tumors should be mentioned. The first postulates that the underlying etiologic factor is irritation by mechanical means or infection. As Raiford has pointed out, the portions of the gastrointestinal tract in which irritation is most likely to occur are those in which there is the most stasis. In the small intestine, stasis and irritation reach their highest level in the duodenum and the terminal ileum. It is at these areas that tumors, both benign and malignant, are most frequently found. Cattell and Pyrtek [7] stated: "It is our feeling that these polyps represent an adenomatous type of hyperplasia as a reaction to inflammation specifically a duodenitis."

The second theory is that of Cohnheim, which has at its basis the arrested development of misplaced embryonic tissue which later takes on new growth. Schottenfeld [8] has questioned whether this theory would apply to the small intestine, since this organ does not develop until the last four months of fetal life. Raiford, however, has suggested that this delayed growth allows less opportunity for misplacement of embryonic tissues and may possibly explain the relative rarity of tumors of the small bowel as compared with their frequency in the colon and stomach.

Most benign tumors of the duodenum are intrinsic and extend toward the bowel lumen. They may be polypoid, pedunculated, or sessile.

The commonest benign tumor of the duodenum is the adenoma. The usual "benign polyp" or papilloma falls into this class. It is usually a small pedunculated lesion and seldom causes symptoms until it becomes eroded with secondary hemorrhage. Rarely does this tumor attain sufficient size to cause obstruction. An adenoma is usually a single lesion, but multiple lesions may occasionally be found. Pathologically the adenoma is found to consist of a soft mass of glandular tissue with a connective-tissue stroma. Raiford [5] has defined it as "a benign hypertrophy of the glandular epithelium of the mucous membrane." It may consist of either a mass of Brunner's glands or a hypertrophied area of intestinal glands. The former type is

4. Golden, R.: Non-Malignant Tumors of the Duodenum: Report of 2 Cases, Am. J. Roentgenol. **20**:405-413 (Nov.) 1928.

5. Raiford, T. S.: Tumors of the Small Intestine, Arch. Surg. **25**:122-177 July; 321-355 (Aug.) 1932.

6. Weber, H. M., and Kirklin, B. R.: Roentgenologic Manifestations of Tumors of the Small Intestine, Am. J. Roentgenol. **47**:243-253 (Feb.) 1942.

7. Cattell, R. B., and Pyrtek, L. J.: Multiple Polyps of the Duodenum, Lahey Clin. Bull. **6**:73-79 (Jan.) 1949.

8. Schottenfeld, L. E.: Lipomas of the Gastrointestinal Tract with Special Reference to the Small Intestine Including the Ileum: Review of the Literature and Report of 6 Cases, Surgery **14**:47-72 (July) 1943.

usually found in the first portion of the duodenum because of the prevalence of Brunner's glands in that area. Rarely does malignant change occur in these lesions as in the cases reported by Finney and Finney [9] and by Botsford and Seibel.[10] The incidence of malignant change is much lower than is found in polypi of the colon. Raiford does not believe that polyps are predestined to malignant change but that they are more susceptible to irritative processes because of an abnormal mechanical arrangement.

Tumors of smooth-muscle origin are seen not infrequently in the gastrointestinal tract, but most of them occur in the stomach. Golden and Stout [11] found that only 5% of all gastrointestinal leiomyomas occurred in the duodenum, and that one-third of these were malignant. Unlike those occurring in the stomach, myomas originating in the small intestine are often extrinsic in growth; thus perforation is more frequent in the latter group. Hemorrhage resulting from ulceration of the tumor is the commonest symptom of a myoma located in the duodenum. The histology of this type of tumor is much like that of smooth-muscle tumors found elsewhere.

The fibroma is a rare tumor and is seldom found in the duodenum. It is rather small and rarely causes symptoms. It may be sessile, pedunculated, or extrinsic, depending upon its point of origin in the bowel wall. The mucous membrane is often found to be intact over a mass which is firm and rubbery, and the cut section has a gray-white color. Fibromas usually arise from connective-tissue cells of the subserosa or the submucosa, but in rare instances they originate in the periarterial connective tissue.

The lipoma is a soft yellow nodule, which is not usually found until autopsy because it seldom causes symptoms. It is often attached by a long slender pedicle, which occasionally breaks and results in the tumor sometimes passing through the rectum. This type of tumor also occurs more frequently in the ileum and less commonly in the duodenum. Bleeding is sometimes seen, and the tumor may become of sufficient size to cause obstruction and, in the jejunum and ileum, intussusception. Microscopically it is found to consist of fat cells separated by thin layers of connective tissue. Comfort [12] reported that symptoms were produced in only three of the 15 recorded cases of duodenal lipoma reviewed by him.

Another rare and interesting tumor of the small bowel that also occurs infrequently in the duodenum is the angioma. Angiomas are of two types, the hemangioma and the lymphangioma. The principal symptom of intestinal hemangioma is hemorrhage, and because the tumor is usually small, it may be exceedingly difficult to locate either by roentgenographic studies or by surgical exploration. Carman,[13] however, reported a case in which the tumor attained sufficient size to cause duodenal obstruction. Hemangiomas are found to consist of endothelium-lined spaces filled with blood and fibrin. The lymphangiomas are similar to hemangiomas, but the spaces are filled with a gelatinous pink-staining material from the lymph. The

9. Finney, J. M. T., and Finney, J. M. T., Jr.: Papilloma of the Duodenum, Ann. Surg. **93**:294-300 (Jan.) 1931.

10. Botsford, T. W., and Seibel, R. E.: Benign and Malignant Tumors of the Small Intestine, New England J. Med. **236**:683-694 (May 8) 1947.

11. Golden, T., and Stout, A. P.: Smooth Muscle Tumors of the Gastrointestinal Tract and Retroperitoneal Tissues, Surg., Gynec. & Obst. **73**:784-810 (Dec.) 1941.

12. Comfort, M. W.: Submucous Lipomata of the Gastrointestinal Tract, Surg., Gynec. & Obst. **52**:101-118 (Jan.) 1931.

13. Carman, R. D.: Hemangioma of the Duodenum, Am. J. Roentgenol. **8**:481-482 (Aug.) 1921.

angiomas may arise from the submucous, the intramuscular, or the subserous vascular plexuses but more commonly originate from the submucous vessels.

Booher and Pack [14] were able to find 12 reported cases of enterogenous cysts of the duodenum and added one from their own experience. The lesions are found most frequently in infants. Because the symptoms are caused by obstruction, the preoperative diagnosis is usually pyloric stenosis. These authors point out that the surgical treatment should consist of removal of the cyst and its attached portion of bowel because damage to the blood supply of the involved area is likely to ensue if local removal is attempted. Enterocysts in the duodenum are usually internal in type, but the reverse is true when they occur in the ileum. At microscopic examination they are found to be composed of cells from all layers of the intestinal wall. Cystic changes rarely occur in adenomas arising from Brunner's glands, and such tumors are easily removed by enucleation.

Aberrant pancreatic tissue is not infrequently found in the duodenum [15] as a small rest lying beneath the mucosa. It does not seem to us that a pancreatic rest should be classified as a tumor, since it is not neoplasm but a depository of displaced normal tissue.

Hemorrhage is the most frequent symptom of a benign tumor of the duodenum.[16] In the series reported by Olson, Dockerty, and Gray,[17] bleeding was present in 54% of the patients who had symptomatic benign duodenal lesions. Dixon and his associates [18] found bleeding to occur in only 12% of 49 patients with malignant duodenal tumors. Hematemesis, melena, or both may be present. Two of our patients who had lesions in the first portion of the duodenum had only melena. The third, who had a neoplasm in the third part of the duodenum, had both melena and hematemesis. Blood loss may be marked but is usually not as great as that occurring with severely bleeding peptic ulcers. Hemorrhage occurs in a higher percentage of tumors of muscular origin than in the other benign neoplasms.

Obstruction and intussusception of the jejunum and ileum are common findings in benign tumors of that portion of the small intestine but are only rarely found complicating benign lesions of the duodenum. Carman's case of a hemangioma causing obstruction in the first portion of the duodenum was the only instance of duodenal obstruction resulting from a benign lesion which Olson, Dockerty, and Gray could find that had occurred at the Mayo Clinic. On the other hand, 76% of malignant tumors of the duodenum produced obstruction.[18] Bookman [19] and Kellogg [20] described duodenal adenomas causing intussusception.

---

14. Booher, R. J., and Pack, G. T.: Cysts of the Duodenum, Arch. Surg. **53**:588-602 (Nov.) 1946.

15. Barbosa, J. J. deC.; Dockerty, M. B., and Waugh, J. M.: Pancreatic Heterotopia: Review of the Literature and Report of 41 Authenticated Surgical Cases, of Which 25 Were Clinically Significant, Surg., Gynec. & Obst. **82**:527-542 (May) 1946.

16. Balfour, D. C., and Henderson, E. F.: Benign Tumors of the Duodenum, Ann. Surg. **89**:30-35 (Jan.) 1929.

17. Olson, J. D.; Dockerty, M. B., and Gray, H. K.: Benign Tumors of the Small Bowel, Ann. Surg. **134**:195-204 (Aug.) 1951.

18. Dixon, C. F.; Lichtman, A. L.; Weber, H. M., and McDonald, J. R.: Malignant Lesions of the Duodenum, Surg., Gynec. & Obst. **83**:83-93 (July) 1946.

19. Bookman, M. R.: Papilloma of the Duodenum, Ann. Surg. **91**:626-629 (April) 1930.

20. Kellogg, E. L.: Intussusception of Duodenum Caused by Adenoma Originating in Brunner's Glands, M. J. & Rec. **134**:440-442 (Nov. 4) 1931.

Other symptoms of benign duodenal tumor are of a less characteristic nature and consist of various types of vague upper abdominal distress somewhat similar to those found with peptic ulcer. Nausea, belching, and, occasionally, vomiting may be present. Frequently the patient complains of epigastric pain of an unusual type. Because of the resemblance of the symptoms to those of peptic ulcer, the lesions are frequently found after an upper gastrointestinal roentgenographic study. The tumors may also simulate disease of the biliary tract or of the pancreas.

As stated previously, diagnosis of a benign duodenal tumor is often difficult. It can be definitely established only by roentgenographic examination. Roentgenographic studies typically show a central radiolucent filling defect (Fig. 4), which may be circular, vacuolar, or multilocular, lying within and surrounded by the barium shadow of the duodenal bulb. It is often impossible to differentiate between benign and malignant lesions. Frequently, however, as in our first two cases, no abnormality of the duodenum can be found even upon repeated examination. The diagnosis must then be made by surgical exploration.

In the absence of intestinal obstruction, hematemesis indicates bleeding proximal to the ligament of Treitz. If melena has been the only evidence of bleeding, the jejunum and ileum must also be carefully examined. It is well to remember that bleeding occurs much more frequently from tumors of the duodenum than from those in the remaining part of the small bowel. If a definite source of the hemorrhage cannot be found, the exploration should include a duodenotomy and careful palpation of the duodenal mucosa. If this procedure had been performed at the first operation in Case 1, the lesion would have been found, and if it had not been done in Case 2, the tumor would certainly have been overlooked.

The decision as to the best method of treatment for duodenal lesions in which hemorrhage or obstruction has occurred is not difficult. Most of the benign tumors can be easily excised by surgical exploration of the duodenum, ligation of the pedicle, and removal of the lesion. It is advisable to have a frozen section made because of the possibility of malignant change in a benign-appearing lesion.

Polyps that are found in the duodenum during the course of operation should also be removed, for removal adds little to the time or the risk of the surgical procedure.

The course to pursue after a benign-appearing duodenal lesion, which does or does not show symptoms or complications that in themselves warrant surgical intervention, has been demonstrated by roentgenologic examination is quite clearly defined. After the diagnosis by the roentgenologist of a benign duodenal polyp, it is unwise to delay operation until gastrointestinal symptoms become severe or other complications occur.

SUMMARY

The case histories of three patients with benign duodenal neoplasms have been outlined. Two of these patients had severe unexplained hemorrhage from the upper gastrointestinal tract for several years before the correct diagnosis was made. The third had moderate hemorrhage complicating cholelithiasis. The lesions were all easily removed transduodenally. Two of the polypoid tumors were found to consist of adenomas of Brunner's glands and the third of an adenoma of the intestinal glands.

A brief outline of the various pathologic forms of benign duodenal tumors has been presented.

VARIATIONAL ANATOMY OF THE HEPATIC, CYSTIC, AND RETRODUODENAL ARTERIES

A Statistical Analysis of Their Origin, Distribution, and Relations to the Biliary Ducts in Two Hundred Bodies

NICHOLAS A. MICHELS, D.Sc.
PHILADELPHIA

IN VIEW of the great advances that have been made in recent years in abdominal surgery, especially as regards the supramesocolic organs, as instanced in cholecystectomy, cholangiojejunostomy with partial hepatectomy, total and subtotal gastrectomy, esophagoduodenostomy, pancreaticoduodenal resections, and ligation of the hepatic artery in cirrhosis, a more extensive and complete knowledge of the variational anatomy of the arteries supplying the upper abdominal organs than that obtainable in standard textbooks of anatomy is urgently needed.

Arterial like other anatomic variations cannot be ignored, for the risks of ligating the wrong vessel or of severing an essential organ-sustaining artery, along with the dangers of ischemia and gangrene, of leaking and bleeding from sites of repair and at anastomotic suture lines, are too great, being ubiquitous possibilities. Arterial variations are verifiable facts of human constitution that have been observed time and time again. They can be statistically estimated by dissection of a large series of bodies and should, accordingly, be summed up in the lowest common denominators readily available to the anatomist for teaching and to the surgeon as a guide and precaution in operative procedures.

Many years ago Sir Arthur Keith, now in his 80th year, stressed the fact that in the biliary region, variations in anatomic structures were "rampant," being so numerous and complex as to offer a "defiant challenge to memory." That cholecystectomy is a dangerous operation was forcefully brought to the attention of surgeons, in 1923, by the admonition of the British surgeon, Flint,[1] to wit: "Technically, gallbladder surgery is much the most difficult of any abdominal surgery and inadequate appreciation of the abnormalities of this region does not lessen the risk."

This warning of Flint is supported by Lahey,[2] who only recently (1948) stated that "We should publicize the fact that cholecystectomy is a dangerous operation.

Aided by a grant from the American Philosophical Society.

From the Daniel Baugh Institute of Anatomy, of the Jefferson Medical College of Philadelphia.

Read before the Section on Surgery, General and Abdominal, at the One Hundred and First Annual Session of the American Medical Association, Chicago, June 11, 1952.

1. Flint, E. R.: Abnormalities of the Right Hepatic, Cystic, and Gastroduodenal Arteries, and of the Bile Ducts, Brit. J. Surg. **10**:509, 1923.

2. Lahey, D. H., in discussion on paper of Wilson and Gillespie, Ann. Surg. **129**:763, 1948.

It is dangerous unless one realizes how important it is to control the blood supply, to demonstrate definitely the anatomic relationships and to realize that anomalous anatomy is very common."

A knowledge of the anatomic variations in the biliary region and how they are brought about affords the surgeon guidance and self-confidence and rewards him in most instances with successful operative results, for obviously the best way to avert injuries to blood vessels is to know them. Angulation of an artery due to traction in the mobilization of the hepatic pedicle or of an enteric segment, like the duodenum, should present no difficulty once the regional artery and its mode of distribution is known and has purposefully been checked.

LITERATURE

Since the publication of Vesalius' "De humani corporis fabrica," at Basle, in 1543, which marked the beginning of modern anatomy, only four books on arterial variations, as observed in the entire human body, have been published, viz., by Haller,[3] in 1756; by Tiedemann,[4] in 1822; by Quain,[5] in 1844, and by Adachi,[6] in 1928, the latter alone having depicted variational patterns of the celiac axis, classifying them into 6 types with 28 subgroups.

Extensive and statistically well-analyzed contributions on the arteries in the hepatic pedicle, especially of the cystic arteries, were made by Flint,[1] Thompson,[7] Browne,[8] and most recently by Daseler, Anson, Hambley, and Reimann.[9] Instructive information on the hepatic and cystic arteries is contained in the works of Brewer,[10] Lipshutz,[11] Adachi,[6] and Behrend.[12] Recent studies on the arteries of the pancreas and duodenum are those contributed by Petrén,[13] Edwards,[14] Pierson,[15] and Woodburne and Olsen.[16]

MATERIAL AND TERMINOLOGY

The present contribution is but an excerpt of my major investigative work on the blood supply of the upper abdominal organs, soon to be published in atlas form

3. Haller, A.: Icones anatomicae, Gottingae, Abram Vandenhoeck, 1756.
4. Tiedemann, F.: Tabulæ arteriarum corporis humani, Carlsruhæ, C. F. Müller, 1822.
5. Quain, R.: The Anatomy of the Arteries of the Human Body, London, Taylor and Walton, 1844.
6. Adachi, B.: Das Arteriensystem der Japaner, Tokyo, Kenkyusha Press, 1928.
7. Thompson, I. M.: On the Arteries and Ducts in the Hepatic Pedicle: Study in Statistical Human Anatomy, Univ. California Publ. **1**:55, 1933.
8. Browne, E. Z.: Variations in Origin and Course of the Hepatic Artery and Its Branches, Surgery **8**:424, 1940.
9. Daseler, E. H.; Anson, B. J.; Hambley, W. C., and Reimann, A. F.: Cystic Artery and Constituents of the Hepatic Pedicle, Surg., Gynec. & Obst. **85**:47, 1947.
10. Brewer, G. E.: Some Observations upon the Surgical Anatomy of the Gallbladder and Ducts, Baltimore, Johns Hopkins Press, 1900, p. 337.
11. Lipschutz, B.: Composite Study of the Coeliac Axis Artery, Ann. Surg. **65**:159, 1917.
12. Behrend, M.: Diseases of the Gallbladder and Allied Structures, Philadelphia, F. A. Davis Company, 1927, and 1947.
13. Petrén, T.: Die Arterien und Venen des Duodenums und des Pankreaskopfes beim Menschen, Ztschr. Anat. u. Entwcklngsgesch. **90**:234, 1929.
14. Edwards, L. F.: Retroduodenal Artery, Anat. Rec. **81**:351, 1941.
15. Pierson, J. M.: Arterial Blood Supply of the Pancreas, Surg., Gynec. Obst. **77**:426, 1943.
16. Woodburne, R. T., and Olsen, L. L.: Arteries of the Pancreas, Anat. Rec. **111**:255, 1951.

with colored plates and extended text. The entire work is based on an examination, over a period of six years, of 200 bodies in our dissecting room. In each instance I personally dissected the arteries supplying the supramesocolic organs and made sketches of them prior to their manipulation by students. The final details of terminal ramifications of the regional arteries, especially of the hepatic and cystic arteries, were worked out in excised specimens, these comprising in all instances the supramesocolic organs en bloc. To avoid preconceived categorization, the difficult, at times baffling, statistical estimates were made only after all sketches had been completed. Of the 200 bodies statistically analyzed, 181 were men, 19 were women. Ages varied from 25 to 90 years, the majority of subjects being over 50 years. In all instances the arteries had been injected with a starch mass colored with carmine red.

Terminology.—In reading previous investigations on the hepatic blood supply, one is impressed with the looseness and nonuniformity of meaning with which the term "accessory hepatic" has been used, most authors having failed to state whether the accessory hepatic is really an accessory or whether it is a replaced hepatic artery, i. e., one taking the place of the normal hepatic artery and arising from a source other than the celiac artery. Percentages as regards accessory hepatic arteries have very little significance and meaning unless it is definitely stated what kind of hepatic is meant by the term "accessory." To clarify this situation the following nomenclature of the hepatic arteries is used.

A typical "normal" hepatic artery arises from the celiac artery and divides into three main branches, the right hepatic, left hepatic, and middle hepatic, the latter supplying the quadrate lobe. The middle hepatic artery is usually a branch of the right or left hepatic and arises in about equal proportion (45%) from either stem. It is not described in texts of anatomy or surgery, but in view of its constancy and the fact that in instances it gives rise to a cystic artery, it should be included in all texts.

When a hepatic artery arises from a source other than the terminal end of the celiac trunk, it is considered an aberrant hepatic artery, of which there are two types, replaced and accessory. A replaced hepatic artery is a substitute for the normal celiac hepatic, which is lacking; an accessory hepatic artery is additive to the celiac hepatic normally present.

The term, "supraduodenal" designates the artery of Wilkie,[17] which supplies the upper border and anterior and posterior surfaces of the first inch of the duodenum, the area corresponding roughly to the anemic spot of Mayo.[18] The term "retroduodenal" connotes the artery which forms a scalloped arcade on the back of the head of the pancreas, with branches to the entire posterior surface of the duodenum. It is synonymous with the cumbersome and confusing term the posterior superior pancreaticoduodenal, which was applied to this textually unlisted artery by Petrén,[13] and was subsequently used by Pierson,[15] and by Woodburne and Olsen[16] to distinguish it from the superior pancreaticoduodenal, anterior in position and well known to surgeons.

Another textually unlisted artery that supplies the back of the pancreas in the neck region and which can readily be found behind the junction point of the superior

17. Wilkie, D. P. D.: Blood Supply of the Duodenum with Special Reference to the Supraduodenal Artery, Surg., Gynec. & Obst. **13**:399, 1911.

18. Mayo, W. J.: Anaemic Spot on the Duodenum, Surg., Gynec. & Obst. **6**:600, 1908.

mesenteric vein and the splenic vein is termed the dorsal pancreatic. Finally, the unlisted artery coursing along the inferior surface of the pancreas, at the tail end of which it anastomoses with a branch of the splenic, is termed the transverse pancreatic artery.

OBSERVATIONS

Celiac Artery

The conventional textbook description of the arterial blood supply of the liver effected through a celiac artery having three branches (hepatic, left gastric, and splenic) occurs in only about one-half the population (55% in 200 bodies), while that of the gall bladder (by a single cystic from a celiac right hepatic in the cystic triangle of Calot) occurs in only 63%. The main causes for this amazing deviation from the so-called normal are the varied anatomy of the celiac artery and the varied sites of origin of the right and left hepatics, be these accessory or replaced. When typical and complete, the celiac artery has three branches, the left gastric, the splenic (lienal), and the hepatic, constituting a complete hepatolienogastric trunk (65% in 200 bodies). This trunk may be incomplete when the right, middle, or left hepatic artery arises from some other source, thereby constituting an incomplete hepatolienogastric trunk. Hence, in a complete or incomplete form a hepatolienogastric trunk occurs approximately in 90%, all other types of celiac trunks comprising the remaining 10%. The celiac may omit the left gastric forming a hepatolienal trunk (3.5%), or the hepatic, forming a lienogastric trunk (5.5%), or the splenic, forming a hepatogastric trunk (1.5%).

Additive branches of the celiac artery comprise the dorsal pancreatic (22%), inferior phrenics (74%), middle colic or an accessory middle colic (3 cases). Frequently, there is no celiac hepatic artery. In this series the common hepatic artery was replaced from the superior mesenteric in five bodies, from the aorta in three bodies, and in one body from the left gastric. The tripod of Haller occurred in 25%, a tetrapod (formed by addition of the dorsal pancreatic), in 5%.

Aberrant Hepatic Arteries

An aberrant hepatic artery, as stated, arises otherwise than from a typical celiac hepatic. Aberrant hepatic arteries comprise two types, viz., replaced and accessory, the former being substitutive, the latter additive, vessels.

Replaced right hepatic arteries take origin predominantly from the superior mesenteric, less seldom, from the aorta, gastroduodenal, retroduodenal, superficial cystic, or dorsal pancreatic. Replaced left hepatic arteries arise, nearly exclusively, from the left gastric or from the superior mesenteric via a replaced hepatic trunk (5 cases). Accessory hepatic arteries take origin from various sources, the accessory right hepatics arising predominantly from the superior mesenteric and the accessory left hepatics from the left gastric.

From the statistics gathered in this study, it may be estimated that in over one-half the population an aberrant hepatic artery does not occur. Of the 200 bodies investigated, 83 (41.5%) had one or more aberrant hepatics, while 117 bodies (58.5%) had none. A total of 106 aberrant hepatics were found in the 83 bodies having them. Sixty-three (31.5%) had I aberrant vessel (accounting for 63); 17 bodies (8.5%) had two (accounting for 34), and 3 bodies (1.5%) had three (accounting for 9). The marked differences in the percentages of aberrant and

accessory right hepatics recorded in the literature are due, in part, to the failure of authors to differentiate between the total number of aberrant hepatics observed in the sample they investigated (50 or 100 bodies) and the number of bodies actually having an aberrant hepatic. The present statistical analysis supports the conclusion that some sort of an aberrant hepatic artery (replaced or accessory) occurs in approximately every other body (41.5%) and that 31.5% have but one aberrant hepatic artery, while 10% have two or more.

An analysis of the types of aberrant hepatic arteries encountered showed that of the 52 (26%) aberrant right hepatics observed, 36 were replaced, and 16 were accessory. Of the 54 (27%) aberrant left hepatics encountered, 31 were replaced, and 23 were accessory.

The above data may be tabulated as follows:

	Bodies	
	No.	%
Aberrant right hepatic arteries in 200 bodies		
Replaced	36	18
Accessory	16	8
Total	52	26
Aberrant left hepatic arteries in 200 bodies		
Replaced	31	15.5
Accessory	23	11.5
Total	54	27.0

Because of the frequent origin of the left hepatic artery (replaced or accessory) from the left gastric, the early anatomists followed the nomenclature which Haller [3] suggested in 1745, and designated the left gastric as the gastrohepatic artery, a term still used in current French texts. Of the 46 bodies with an aberrant left hepatic arising from the left gastric artery, 23 were replaced, 23 were accessory. Hence, functionally considered, one-half the aberrant left hepatics from the left gastric constitute the only left hepatic present, severance of which during gastric resection may lead to ischemia and subsequent necrosis of the left lobe of the liver.

Of the 34 bodies having an aberrant right hepatic from the superior mesenteric, 25 were replaced, and only 9 were accessory, indicating that roughly three-fourths of the aberrant right hepatics arising from the superior mesenteric (17% incidence, including replaced hepatic trunks) are replaced, i. e., the only right hepatic present. The inexcusable ligation of such an artery during cholecystectomy would deprive the right lobe of its blood supply and may readily be the direct cause of grave morbidity and death, as stated by Gordon-Taylor.[19] Severance of a common hepatic artery of superior mesenteric origin (5 cases) during pancreaticoduodenal resections or of a common hepatic trunk arising directly from the left gastric (one case) would result in immediate death of the patient.

Despite the complexity and varied character of the hepatic arterial blood supply, any sample of it may, with minor modifications, be classified into 1 of the following basic types.

The celiac hepatic artery supplies the following branches:

1. The right, left, and middle hepatic (textbook type and present only in about half the subjects, 55% (Fig.1)

19. Gordon-Taylor, G.: Rare Case of Severe Gastrointestinal Hemorrhage with a Note on Aneurysm of the Hepatic Artery, Brit. M. J. **1**:504, 1943.

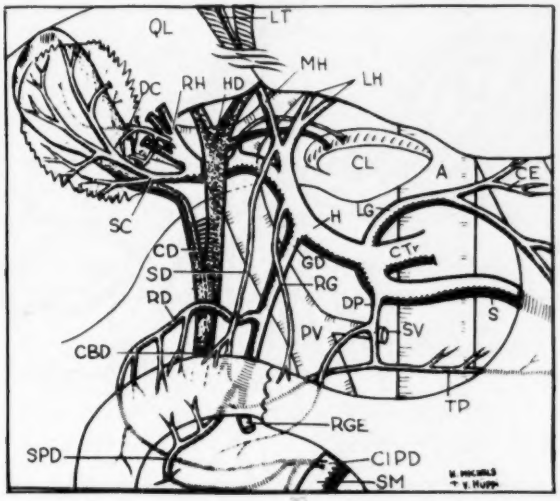


Fig. 1 (Type 1).—Celiac hepatic artery supplies the three typical liver branches, right, left, and middle hepatic, latter for quadrate lobe; hepatolienogastric-celiac trunk. Double cystic, superficial (*SC*) and deep (*DC*) branch arising separately in Calot's triangle, deep being high. Long (6 cm.) parallel cystic duct (*CD*) swerving posteriorly. Retroduodenal artery (*RD*) forming posterior pancreaticoduodenal arcade. Supraduodenal artery of Wilkie to first inch of the duodenum. Dorsal pancreatic (*DP*) to neck, and transverse pancreatic (*TP*) to inferior surface of pancreas. Accessory hepatic duct from left side (caudate lobe, *CL*).

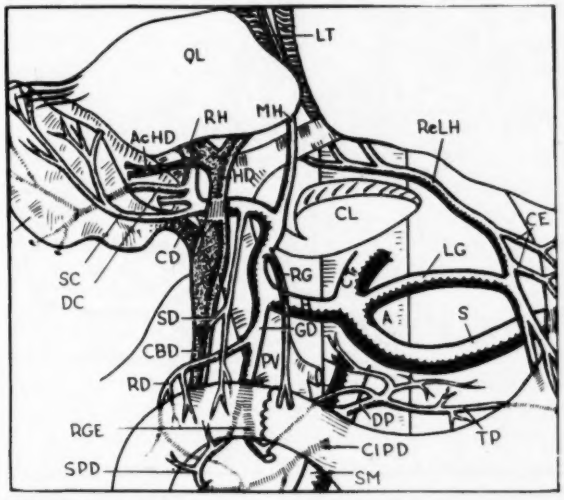


Fig. 2 (Type 2).—Replaced left hepatic artery from left gastric, celiac suppying only right hepatic and middle hepatic. Dual cystics between which is a liver branch. Accessory hepatic duct (*AcHD*) near deep cystic (*DC*), joining right branch of hepatic duct. Dorsal pancreatic (*DP*) from superior mesenteric. Retroduodenal (*RD*) ending in a common inferior pancreaticoduodenal.

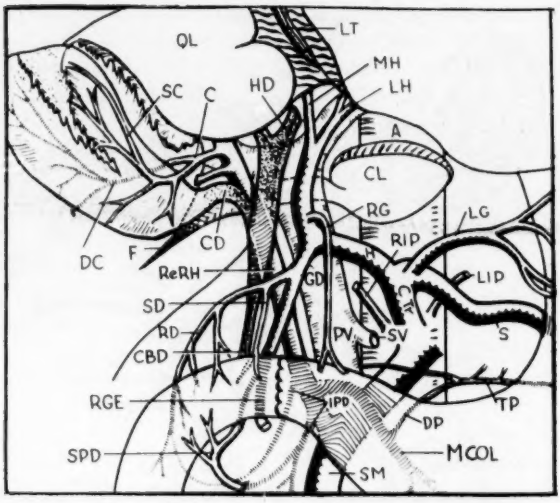


Fig. 3 (Type 3).—Replaced right hepatic artery from superior mesenteric. Celiac artery supplying only middle hepatic and left hepatic. Middle colic (*MCOL*) arising from replaced right hepatic and giving off dorsal pancreatic (*DP*). Single cystic (*C*) from replaced right hepatic bifurcating into a superficial and deep branch, the gamellae cysticae of Vesalius. Liver branch to fissured area under gall bladder (*F*). Anterior and posterior pancreaticoduodenal arcades here uniting with replaced right hepatic and not with superior mesenteric.

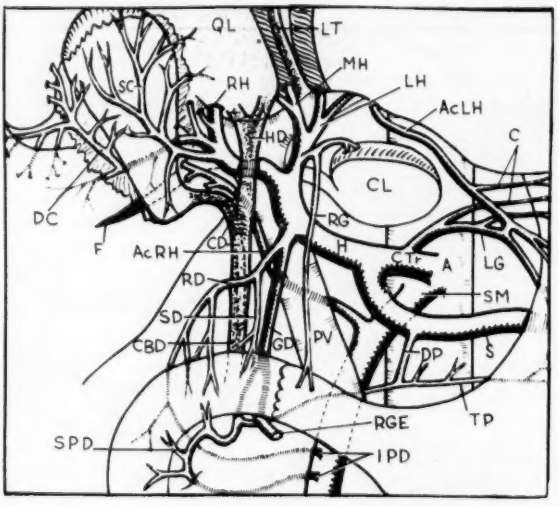


Fig. 4 (Type 7).—Liver has five major arteries, three hepatics from the celiac, an accessory right hepatic from superior mesenteric, and an accessory left hepatic from left gastric, hence, three sources of blood supply. Cystic duct swerves posteriorly to hepatic duct with which it becomes united. Note how an aberrant right hepatic from superior mesenteric supplies fissured area under gall bladder (*F*) and may be mistaken for the cystic artery, which in many instances actually arises from such an artery. Dual cystics, the deep branch (*DC*) continuing as a liver artery. Retroduodenal (*RD*) has its own inferior pancreaticoduodenal.

2. The right hepatic and middle hepatic—the left hepatic replaced from the left gastric, 10% (Fig. 2)

3. The left hepatic and middle hepatic—the right hepatic replaced from the superior mesenteric, 11% (Fig. 3)

4. Only the middle hepatic—the right hepatic replaced from the superior mesenteric, the left hepatic replaced from the left gastric (1%)

5. The right, middle, and left hepatic—left hepatic small, hence, an accessory left hepatic from the left gastric (8%)

6. The right, middle, and left hepatic—right hepatic small, hence, an accessory right hepatic from the superior mesenteric, etc. (7%)

7. The right, left, and middle hepatic, small or of usual size. There is an accessory right hepatic from the superior mesenteric and an accessory left hepatic from the left gastric, 1% (Fig. 4)

8. Combination patterns of a replaced right hepatic and accessory left hepatic or the reverse, an accessory right hepatic with a replaced left hepatic (2%).

When the celiac hepatic artery was absent, the hepatic trunk was derived from one of two sources:

1. The superior mesenteric artery (five cases)
2. The left gastric artery (one case)

Cystic Artery

Typically, the cystic artery arises from the celiac right hepatic to the right of the hepatic duct in Calot's triangle, the boundaries of which are, inferolaterally, the cystic duct; medially, the hepatic duct, and cephalad, the liver (Fig. 1). The right hepatic and the cystic artery are predominantly located in the upper part of the triangle, the right hepatic having crossed under or over (12%) the hepatic duct to reach the triangle. If, in any subject, the surgeon is in doubt as regards the identity of the structures, a careful dissection or creation of this triangle will, in most instances, effect correct orientation.

The course of the cystic artery in the triangle may be short or long, depending on its site and mode of origin. On reaching the gall bladder it usually bifurcates into its characteristic superficial and deep branch, the cysticae gemellae, which Vesalius spoke of in 1564 (Fig. 3). The superficial branch is distributed to the free peritoneal surface of the gall bladder; the deep branch courses behind the gall bladder to become distributed to its attached nonperitoneal surface and to the gall bladder bed.

The superficial and deep cystic branches are anastomosed at various points on the gall bladder, and both emit a variable number of twigs to the liver substance, sometimes more to the right than to the left side of the gall bladder or vice versa. Quite frequently such twigs are no longer twigs but vessels of appreciable size. A few cases were encountered in which, respectively considered, the superficial, the deep, or both cystic branches, after supplying the gall bladder, entered the liver as major liver arteries (Fig. 4).

Double Cystic Artery.—In about one-fourth the population, the gemellae cysticae, i. e., the superficial and deep branches of the cystic artery, have a separate origin, the deep cystic commonly arising from the right hepatic in the triangle, the superficial from the right hepatic to the left of the hepatic duct or from some other source, such as the middle hepatic, left hepatic, gastroduodenal, and retroduodenal. Dual

cystics, accordingly, are not fortuitous anomalies but constitute a prevalent mode of blood supply to the gall bladder, having been observed in 50 of the 200 (25%) specimens investigated (Figs. 1, 2, and 4).

This percentage of dual cystics is considerably higher than that reported by Lipshutz [11] (10%), Daseler and co-workers [9] (14%), Flint [1] (15%), and Browne [8] (21%) and is due to the fact that I dissected the hepatic branches up to their very entry into the liver, thereby on many occasions finding a high hidden cystic, which usually turned out to be the deep branch (Fig. 1). Furthermore, in many cases the points of origin of the two cystics from the right hepatic were so close as to simulate one cystic, when actually two cystics were present (Fig. 4). Only one triple cystic was observed.

The statistics regarding the various modes of origin of the single and double cystic arteries and regarding the normal and aberrant arteries from which they spring are too long and varied to be recorded here, except in summary. Of great import in the quest for the cystic is the fact that in nearly 20% of the 200 cases no cystic artery had its origin in Calot's triangle, while in 80% there was always an origin of a cystic in the triangle, either the single cystic, or the superficial or deep branch, or both branches. Cystics arising from the typical celiac right hepatic in the triangle comprised single cystic 43%, double 11.5%, either the superficial or the deep branch 8%—a total of 63%. Aberrant right hepatics gave rise to the cystic in the triangle in 18%. The single cystic, its superficial or its deep branch, arose from the right hepatic to the left of the hepatic duct in 19.5%, from the left hepatic, middle hepatic, or common hepatic in 6.5%, and from the gastroduodenal or its retroduodenal branch in 4%. An origin of the cystic, especially the deep cystic, from an aberrant replaced right hepatic from the superior mesenteric occurred more frequently (11%) than from a hepatic of similar origin which was accessory (3 cases). Of the 50 cases with dual cystics, only two did not contain the origin of a cystic from the right hepatic in Calot's triangle.

Biliary Ducts

Variations in the bile ducts are of such frequency and of such pronounced character as to be of vital concern to every surgeon. A disregard of the anomalies, especially of accessory hepatic ducts, courts injury to them, with resultant disconcerting postoperative leakage of bile. That the majority of benign strictures of the common duct are due to surgical injury during cholecystectomy is well known and has recently again been emphasized by Wilson and Gillespie [20] and by Lahey,[2] the latter stressing the fact that injuries are more likely to occur to the hepatic duct than to the common bile duct.

What seemingly is the common bile duct often is not but is rather the hepatic duct firmly united by dense connective tissue with the cystic duct, constituting the well-known short (1 to 3 cm.) and long parallel cystic ducts (6 cm.) (Figs. 1 and 4). The length of the hepatic duct depends on the site of opening of the cystic duct, which may occur anywhere along the duct, even on its anterior aspect and, after a half-circle spiral, on its left side. In cases in which the union of the two ducts has been prolonged to the level of the duodenum (6 cm.) or to a point just above or

20. Wilson, H., and Gillespie, C. E.: Partial Hepatectomy with Intrahepatic Cholangiojejunostomy, Ann. Surg. **129**:756, 1949.

below it, there is usually no supraduodenal portion of the common bile duct, or very little of it (Figs. 1 and 4). Such long-veiled and hidden cystic ducts may not only harbor residual gallstones but because of their abutment to the hepatic duct may lead to an injury of the latter during cholecystectomy.

Accessory hepatic ducts are extremely difficult to define, for none of them is accessory, all being but aberrantly placed low tributaries to the hepatic duct, to its right or left branch, or to the cystic duct itself. In this sense the term "aberrant hepatic duct" is much more appropriate than the term "accessory," as will be shown shortly in a work to be published from this Institute by Dr. Healey and Mr. Schroy, who have outlined and statistically analyzed the bilobar segmental arrangement of the biliary tree, as ascertained in 100 corrosion casts made with vinyl acetate injections.

Following the usual mode of designating an accessory hepatic duct as one which is prone to be injured in biliary surgery, i. e., one coursing in the cystic triangle, in this series of 200 bodies I found 36 cases (18%) of accessory hepatic ducts (Fig. 2). In 10% these accessory ducts joined the hepatic duct, in 3.5%, the right branch of the hepatic duct, and in 1%, the common bile duct. In 2% the cystic duct drained into an accessory hepatic duct which joined the normal hepatic duct. In one case, two accessory hepatic ducts joined the hepatic duct. In another case, one accessory duct joined the right branch of the hepatic duct, the other, the hepatic duct. There were only two cases of an accessory duct arising from the left side, one in which it came from the caudate lobe and joined the hepatic duct (Fig. 1), the other in which it joined the common bile duct, the cystic artery passing between it and the hepatic duct. Of surgical importance is the fact that in many instances an accessory hepatic duct arises or courses under the gall bladder. Filamentous in character, such a duct may be mistaken for strands of fibrous tissue or nerves and can readily be torn or severed during cholecystectomy, causing disconcerting post-operative jaundice.

Retroduodenal Artery

It is in virtue of this textually unlisted artery that the duodenum is the only section of the gut which has a dual blood supply, the retroduodenal artery supplying the back of the duodenum.

Double pancreaticoduodenal arcades, one anterior, the other posterior, to the head of the pancreas and back of the duodenum and made by different arteries, were first described by Haller [3] in his Latin text in 1752. Forgotten because of an indefinite terminology for nearly two centuries, the artery in the back of the duodenum was unsuccessfully resuscitated by Petrén, of Sweden, in 1929, with the long descriptive term, posterior superior pancreaticoduodenal artery. Since this term proved to be too cumbersome to be remembered and since in 10% of the present cases the artery forming the posterior duodenal arcade arose from an artery other than the gastroduodenal, which the superior pancreaticoduodenal rarely does, the term "retroduodenal" is used, being shorter and much more descriptive and indicative than Petrén's term.

Typically, the retroduodenal artery arises as the first collateral branch of the gastroduodenal (Figs. 1, 2, 3, and 4). Its site of origin from the latter lies above, occasionally behind, the duodenum and head of the pancreas and is often cryptic, being hidden by dense fibrous tissue. In its downward course it descends for several

centimeters along the left side of the common bile duct, crosses its supraduodenal portion anteriorly, and again descends for a centimeter or more along the right side of the common duct. At about the middle of the posterior surface of the head of the pancreas behind the intrapancreatic part of the common bile duct, it forms a U-shaped, scalloped posterior pancreaticoduodenal arcade, branches (7 to 10) of which supply all three parts of the duodenum and, to a less extent, the head of the pancreas in the back. In its secondary and tertiary arcades, the posterior pancreaticoduodenal arcade is comparable to the anterior arcade made by the superior pancreaticoduodenal. Both arcades unite with the superior mesenteric or its first jejunal branch via a common inferior pancreaticoduodenal (60%), or each arcade has its own inferior pancreaticoduodenal, that of the posterior arcade, arising at a higher level in back of the pancreas (Figs. 1 and 4).

Ramifications of the retroduodenal about the supraduodenal, retroduodenal, and intrapancreatic portions of the common bile duct account in large measure for the rich vascularization of the common duct, the latter again being crossed near its distal end by several branches from the retroduodenal arcade. The posterior arcade comes to perfect display with the mobilization of the duodenum and removal of a thin film of connective tissue (Toldt's fascia, remnant of the primitive mesoduodenum) that overlies it and the retroduodenal venous arcade. The latter is superficial to the arterial arcade and drains into the portal vein.

The retroduodenal artery is of decided surgical importance for the following reasons: 1. The entire cystic artery (two cases) or its superficial branch (six cases) may arise from it. 2. In incisions of the common duct for removal of stones it may readily be injured, for it crosses its supraduodenal portion anteriorly. 3. End branches of its arcade often cross under the superior mesenteric to supply the first part of the jejunum, a point to be remembered in gastrojejunostomies lest the first part of the small bowel be deprived of its blood supply. 4. In ligations, explorations, and transplantations of the common bile duct, especially of the intrapancreatic portion, the retroduodenal artery should be noted to avoid annoying hemorrhages. 5. In hidden bleeding, which follows spontaneous rupture of the posterior duodenal wall by ulceration, the retroduodenal artery may be involved more than the supraduodenal or gastroduodenal. 6. In many instances it forms a suprapancreatic arcade with the supraduodenal artery of Wilkie or with the right gastric artery, the arcade supplying the critical arterial transition zone between the pylorus and the first part of the duodenum with a fountain-like spray of twigs. 7. It may be anastomosed with the splenic or celiac arteries via a branch of the dorsal pancreatic which passes behind the common bile duct.

ARTERIAL RELATIONS

Relations of the biliary ducts to the right hepatic artery and its branches, especially the cystic, depend on the varied origin and mode of branching (early or late) and the course taken by the right hepatic. The following anatomic facts merit repeated recollection. In nearly 20% of cases the site of origin of the cystic artery is located outside the cystic triangle, i. e., the cystic artery arises to the left of the hepatic duct from the hepatic, right hepatic, middle hepatic, or left hepatic, or from the gastroduodenal and must, accordingly, cross the bile duct system (usually the hepatic duct) to reach the triangle.

In the majority of cases the celiac right hepatic artery crosses the hepatic duct posteriorly, purely ventral crossings having been observed in only 12%. Not infrequently, the right hepatic artery is represented by two branches, one crossing the hepatic duct anteriorly, the other posteriorly. In dual cystics, when the superficial cystic arises from an artery to the left of the hepatic duct (right, middle, or left hepatic), it usually crosses the hepatic duct anteriorly. In such cases the deep cystic may arise in the triangle from an aberrant right hepatic derived from the superior mesenteric which in its ascent to the triangle crossed the common bile duct, often at the junction point of the cystic duct where it may be injured or severed. In 7% of the cases the superficial cystic swung caudally around the proximal end of the cystic duct, i. e., left Calot's triangle to reach the peritoneal surface of the gall bladder, an item to be remembered in locating the superficial cystic. When the entire cystic artery or its superficial branch arises from the gastroduodenal artery or its retroduodenal branch, it must cross the common bile duct and often the cystic duct to reach the gall bladder. This common pattern should be borne in mind, for ordinarily the surgeon does not look for a cystic artery caudal to the cystic duct.

An artery that looks like a cystic and courses near and parallel with the cystic duct is not necessarily the cystic artery.

It may be (1) an early liver branch of the right hepatic (Fig. 3); (2) the lower branch of a right hepatic that bifurcated either in the triangle or before it crossed the hepatic duct, or (3) an aberrant right hepatic from the superior mesenteric or a branch of it being distributed to the fissured area, often found under the gall bladder (Fig. 4). The detected cystic artery may be only one of the cystics because, frequently, the right hepatic artery divides in the triangle into two major branches, one giving off the superficial, the other, the deep cystic artery.

The triangle may contain two right hepatic arteries of different origin, one arising from the celiac right hepatic, the other from the superior mesenteric, the latter and not the former giving off the cystic artery. Approaching the cystic duct, such an aberrant right hepatic may erroneously be ligated instead of the cystic, causing severe damage to the liver (Fig. 4).

In Calot's triangle a right hepatic artery of celiac origin may be high, low, or intermediate in position, depending on where it crossed the hepatic duct and where it courses in the triangle.

Union of the right and left branches of the hepatic duct usually occurs high in the portal fissure but may be retarded, giving rise to a short, low-forked hepatic duct. Through this fork, under or over it, the right hepatic or the cystic artery may pass. The situation may be reversed (high-forked hepatic duct), with similar orientation of the two vessels.

Even after crossing the hepatic duct or the right hepatic duct and left branch at a high level (high-forked hepatic duct), the right hepatic often descends in the cystic triangle to a region which is dangerously close to the cystic duct. The main reason for this is the fact that both inside and outside the triangle, the right hepatic often makes a characteristic caterpillar-like loop (hump), the convexity of which points downward, upward, to the right, or to the left. In cholecystectomies such sinuosities of the right hepatic are extremely vulnerable, for the cystic may arise from the distal or proximal end of the loop, in the latter instance crossing it, usually anteriorly.

Arterial relations to accessory hepatic ducts are often surgically dangerous and difficult to analyze (Fig. 2). Since an accessory hepatic duct can traverse any part of the cystic triangle, the course of the right hepatic and site of origin of the cystic may be above or below it. A high cystic may cross a low accessory hepatic duct and vice versa. Fortunately, most of the accessory hepatic ducts joining the right branch of the hepatic duct are sufficiently high to be removed from surgical harm, but those joining the cystic duct or running parallel to it decidedly are not. Extremely vulnerable is an accessory hepatic duct which joins the common bile duct below the cystic duct.

COMMENT

In conclusion it may be stated that the relations of the right hepatic and of the cystic artery to the biliary ducts are far too varied and complicated to be remembered individually by the surgeon. Since each case is different, each case merits careful and purposeful inspection. From this study of anatomic relations learned by years of painstaking dissection and from the successful procedure of experienced surgeons, there ensues but one logical conclusion, viz., that the cystic artery should be looked for on the gall bladder itself. Since the superficial cystic ramifies on the free peritoneal surface of the gall bladder, where it can readily be seen by following it medially and caudally, the deep cystic, in the majority of cases, comes to view. If not, then most likely two cystics are present, i. e., the gemellae cysticae have different sites of origin, the deep cystic often being high and hidden in the upper part of Calot's triangle, the superficial cystic coming from a source other than the celiac right hepatic.

ABSTRACT OF DISCUSSION

DR. PHILIP THOREK, Chicago: It is obvious that this paper dovetails with that of Drs. Rienhoff and Woods. This is brought about by Dr. Michels' discussion of the collateral circulation. Although one might have a classic concept of the arterial distribution to the liver, one must nevertheless bear in mind the numerous patterns which the vascular tree is heir to and which may alter our results. Dr. Rienhoff particularly stressed a specific type of patient, and I believe that this too bears emphasis. He mentioned that hepatic artery ligation should be done for the complications of cirrhosis, namely, esophageal varices and ascites. All of us are familiar with the patient who is bleeding to death from a ruptured esophageal varix, and it is in this type of case that the surgeon wishes to refer the patient to a good internist, and the internist in turn wishes to refer the patient to a good surgeon. One must differentiate therefore between the acute complications and the more chronic case in which the ligation can be performed after a thorough work-up and preparation. In the small series in which I have done hepatic artery ligation, the results, although not conclusive, are nevertheless encouraging. My interest in this subject followed the work of Dr. Warren Cole on ligation of the splenic artery in these poor-risk patients; to date, in 12 such cases I have had no immediate mortality. Dr. Rienhoff and Dr. Berman have reported their results on ligation of both the splenic and the hepatic arteries. This seems a more plausible approach if the patient's condition permits. I agree with Dr. Rienhoff that the liver function tests have not been too informative. Although the clinical results in esophageal varices have been encouraging, I have been unable to demonstrate roentgenologically a reduction in the size of these varices.

Ligation close to the celiac axis is preferred. Collateral circulation is brought about via the right and left gastric arteries, the right and left gastroepiploic arteries, and the superior and inferior pancreaticoduodenal arteries. I feel that ligation of the hepatic artery distal to the gastroduodenal artery is technically more difficult and less efficacious. One must emphasize that this is salvage surgery, and we can only hope for palliation. I feel that as time passes, some classification will result whereby we will know in which cases to give medical treatment and in which cases the response will be best to a portacaval shunt or to hepatic and/or splenic artery ligations.

DR. WARREN H. COLE, Chicago: I was particularly interested in Dr. Michels' presentation because I have been vitally interested in this subject for the past several years.

I should like to reemphasize one point he made, namely, that the anatomy of the biliary tract is different in every person. In fact, trying to set up a normal picture in one's own mind is impossible. All one can do is set up a composite of the commoner types.

This subject has a very definite clinical significance, as Dr. Michels has implied. In the first place if one damages the hepatic artery and ligates it, death will ensue in about half the patients, although the administration of heavy doses of penicillin will minimize this danger. Obviously, if the hepatic artery is cut, one should attempt to suture it. I have heard of two instances in which a severed hepatic artery was repaired, with survival of the patient. The other feature of clinical significance in Dr. Michels' presentation is related to damage to the common duct; this is usually inflicted while the surgeon is trying to control hemorrhage. This hemorrhage usually results from injury to the artery because of vascular anomalies. I think we might emphasize that one should never rely upon one's knowledge of anatomy when dissecting in this region because of frequent anomalies; one must use one's eyes, be very careful, and not be in a hurry when dissecting in this area.

Now regarding anomalies of the cystic artery. You will recall that Dr. Michels said he found an accessory artery in 25% of cases. The danger is that the surgeon will see and ligate one cystic artery and then proceed so rapidly with dissection that the second artery is cut, with production of a hemorrhage which may be difficult to control. As Dr. Michels has stated, this accessory cystic artery usually arises from the hepatic artery just beneath the common duct; after severance, it retracts posterior to the common duct, and blind stabbing with an instrument by the surgeon may result in obstruction of the common duct as the bleeding point is ligated. This is a poor way to control bleeding.

In fact, one should establish a habit of inserting a finger into the foramen of Winslow at the beginning of the operation to locate the hepatic artery so that it can be compressed quickly if hemorrhage from a damaged and retracted cystic artery should take place.

In Dr. Michels' paper there was a very pertinent remark somewhat as follows: "An artery that looks like a cystic and courses near and parallel with the cystic duct, is not necessarily the cystic artery." Indeed, as he has implied, it is usually the hepatic artery; time and time again I have been ready to put a clamp on this artery parallel to the cystic duct only to discover after another investigation that it was the right hepatic. I am sure that every surgeon has had that experience at some time or other.

Aberrant hepatic arteries are important. They may explain why some people survive accidental ligation of the hepatic artery and others die of it. Their absence or presence might explain why the death rate following ligation of the hepatic artery in treatment of cirrhosis is higher in some small series than in others. These anomalous arteries usually are not discovered at the operating table and in small series may explain the difference in mortality rate, as Dr. Reinhoff presented to you earlier.

You will recall that Dr. Michels reported accessory hepatic ducts in about 18% of cadavers. If the surgeon does not see the duct but cuts it and does not ligate it, there will be an escape of bile into the free peritoneal cavity. If the peritoneal cavity is not drained, the bile may collect in enormous quantities and give rise to bile peritonitis. If it collects in small quantities, it is usually located over the common duct and may later result in a stricture of the common duct.

I am sure you agree that Dr. Michels has contributed significantly to the precautions in surgery of the biliary tract by showing us the importance of anomalies; we can profit by these precautions, if we are ever mindful of anomalies while operating on the biliary tract.

DR. I. S. RAVDIN, Philadelphia: I had the pleasure of reading Dr. Michels' paper, and I thought constantly of the admonition which Dr. Lahey has made regarding biliary tract surgery. We have in the last five years had sent to us 31 patients with defects of the common duct for operation. This is a disgrace to American surgery. It merely means that while most surgeons teach that cholecystic surgery is easy, it is difficult. Dr. Michels has had an opportunity to do the most careful type of dissections. He has told us not only that the vasculature, as far as the arterial supply is concerned, varies tremendously but that we should not depend on textbooks for that vasculature with certainty. It must mean that those who think they have

ligated the hepatic artery frequently have not ligated the whole arterial supply to the liver. We have indeed found a difference even in experimental animals, and when we have ligated what we considered the hepatic artery, we have found that only a part of it was ligated.

The situation as regards the common bile duct is an even more serious one, for many of these patients are later subjected to multiple operations, and some are made permanent invalids. The time to repair an injured common duct is at the time the injury occurred, and direct end-to-end anastomosis is, in my opinion, the best method of achieving a permanently good result. The only way to avoid injuries to the common duct during cholecystic surgery is accurately to visualize the junction of the common and the cystic ducts.

Dr. Nicholas A. Michels, Philadelphia: I haven't very much to add except to state that during the many years of my investigative work I had no idea that some day it would culminate into the surgical importance and significance it currently has attained. I just ask you to bear in mind the fact of constitutional variations; particularly bear in mind that often there is a blood supply to the liver from the left gastric artery and that when such a left gastric artery is cut, necrosis of the left lobe of the liver might result. I have had an opportunity for verification at postmortem examination.

Another point to be emphasized is the fact that in 17% of cases the right hepatic artery arises from the superior mesenteric; in its ascent to the gall bladder region it often comes very close to the junction point of the cystic and common hepatic duct, where is may readily be injured.

A third fact to be remembered is that in 20% of cases the cystic artery does not have its site of origin in the cystic triangle but arises from an artery outside it. In such cases it crosses the common hepatic duct anteriorly or ascends from below the cystic duct. In some instances an intestinal artery, the retroduodenal artery, furnishes the blood supply to the gall bladder, supplying either the entire cystic artery or its superficial branch. In the first 50 dissected specimens which I showed to Dr. Shallow, there were several cases in which the cystic artery arose from the gastroduodenal.

A fourth point to be remembered is that in 25% of the cases the cystic artery is double; the superficial and deep cystic arise separately, the deep often being high in the triangle.

No surgeon can possibly remember all these arterial variations. As a safeguard, the cystic artery should be looked for on the gall bladder itself. Here you will find the superficial cystic, which in most cases will lead you to the deep cystic and set you right.

EVALUATION OF TRICHLOROETHYLENE AS AN ANESTHETIC AND ANALGESIC AGENT

WILLIAM K. NOWILL, M.D.

C. RONALD STEPHEN, M.D.

DURHAM, N. C.

AND

PAUL W. SEARLES, M.D., M.S.

BUFFALO

THE INTRODUCTION of a new drug into the field of anesthesiology is frequently received either with marked enthusiasm or marked disapproval. Trichloroethylene is one such drug. In England and Canada, since the report of Hewer, in 1942,[1] trichloroethylene has had wide application for the production of analgesia and light-plane anesthesia, particularly in the obstetrical field. In the United States, its use was somewhat discouraged by the report of Waters, Orth, and Gillespie, in 1943,[2] in which adverse effects on cardiac rhythm were noted. Other controversial reports continued to appear in the literature. Hamilton[3] reported 26 deaths in 284 cases of industrial poisoning by trichloroethylene in German industry. However, Taylor[4] tested trichloroethylene in experimental animals and found no adverse toxicological effects. McAuley,[5] in 1943, reported three instances of postoperative bilateral trigeminal anesthesia in cases in which trichloroethylene had been used by the carbon-dioxide absorption technique. Later authors have concluded that the trigeminal nerve paralysis was a result of the interaction of trichloroethylene with hot soda lime producing dichloroacetylene. Brown-

The obstetrical departments of Duke University Hospital and Millard Fillmore Hospital cooperated in these studies.

Read before the Section on Anesthesiology at the One Hundred and First Annual Session of the American Medical Association, Chicago, June 10, 1952.

Arterial blood studies were obtained with the assistance of Miss Regina Frayser and Dr. John Hickam, of the Duke University Hospital Respiratory Research Laboratory.

Cerebral blood flows and electroencephalographic tracings were obtained with the assistance of Drs. F. Wren and B. Bloor, and the neurosurgical department, Duke University Hospital.

From the Division of Anesthesia, Duke University Hospital, and Duke University School of Medicine, and the Department of Anesthesiology, Millard Fillmore Hospital, and University of Buffalo School of Medicine.

1. Hewer, C. L.: Trichlorethylene as a General Analgesic and Anaesthetic, Proc. Roy. Soc. Med. **35**:463-465, 1942.

2. Waters, R. M.; Orth, O. S., and Gillespie, N. A.: Trichlorethylene Anesthesia and Cardiac Rhythm, Anesthesiology **4**:1-5, 1943.

3. Hamilton, A.: Industrial Toxicology, New York, Harper & Bros., 1943.

4. Taylor, H.: Experiments on the Physiological Properties of Trichlorethylene, J. Indust. Hyg. & Toxicol. **18**:175-193, 1936.

5. McAuley, J.: Trichlorethyelene and Trigeminal Anesthesia, Brit. M. J. **2**:713-714, 1943.

ing,[6] in 1937, reported a case of subacute yellow atrophy of the liver as an industrial poisoning. Other authors [7] have been unable to demonstrate any hepatotoxicity. This divergency of opinion has appeared throughout the literature and has led to much confusion in regard to the toxic properties of trichloroethylene. We therefore decided to attempt evaluation of this drug from the standpoint of alteration of physiology and of clinical use. We have used throughout the entire study specially prepared trichloroethylene, manufactured by Imperial Chemical, Ltd., and marketed by Ayerst, McKenna & Harrison, Ltd., under the trade name of "trilene." A dye, "waxoline blue," to prevent confusion with chloroform, and a preservative, 0.01% thymol, have been added.

CHEMISTRY

Trichloroethylene is a chlorine substituted derivative of ethylene having the structural formula of ClHC=CHCl. It thus resembles both ethylene and chloroform in its formula. In its physical properties, it more resembles chloroform, having a specific gravity of 1.46, a vapor density of 65.75, and a boiling point of 87 C. It has a slightly sweetish odor, similar to that of chloroform, and is noninflammable. When exposed to heat and oxygen, degradation products include phosgene, hydrochloric acid, and dichloroacetylene.

PHYSIOLOGICAL STUDIES

Our physiological studies are divided into four general categories: (1) central nervous system; (2) cardiovascular; (3) liver; (4) renal.

Central Nervous System Studies.—Cerebral blood flow was measured, utilizing a modified Gibbs technique.[8] Five normal adult rabbits and one Macacus rhesus monkey were used. Electroencephalographic tracings and femoral arterial blood pressures were also simultaneously recorded. Trichloroethylene in concentrations varying from 0.1% to 3.5% produced an increase in cerebral blood flow. This increase appeared to be less than that produced by the addition of 5% carbon dioxide to the inhaled oxygen. In one of the animals, high vapor concentration of 3.5% produced a ventricular tachycardia, with a decrease in systemic blood pressure and a decrease in cerebral blood flow.

Electroencephalographic changes, even with the high concentrations of trichloroethylene, were minimal, consisting of a slight slowing and a slight depression of wave height.

Cardiovascular Studies.—Four groups of patients were studied as to electrocardiographic and systemic blood pressure recordings as might be affected by trichloroethylene. The first group consisted of 120 patients in the first stage of obstetrical labor in which trichloroethylene-air mixtures were self-administered by

6. Browning, E.: Toxicity of Industrial Organic Solvents, Report 80, Industrial Health Research Board of the Medical Research Council, London, 1937.

7. Herzberg, M.: Histology of Tissues Taken from Animals Killed by Prolonged Administration of Concentrated Vapors of Trichlorethylene, Anesth. & Analg. **13**:203-204, 1934. Barrett, H. M.; MacLean, D. L., and Cunningham, J. G.: Comparison of the Toxicity of Carbon Tetrachloride and Trichlorethylene, J. Indust. Hyg. & Toxicol. **20**:360-379, 1938. Armstrong, D. M.: Assessment of Liver Damage Following Trichlorethylene and Di-Ethyl Ether Anaesthesia, Anaesthesia **2**:45, 1947.

8. Gibbs, F. A.: Thermoelectric Blood Flow Recorder in the Form of a Needle, Proc. Soc. Exper. Biol. & Med. **31**:141-146, 1933.

the patient, utilizing the cyprane mask. In these cases the cyprane mask was never set above the mark No. 3 (0.5 to 0.6% vapor concentration), and unconsciousness was not produced. In these patients no electrocardiographic and blood pressure changes were noted. In 10 additional patients in whom the cyprane mask was used to produce light anesthesia for the second stage of labor, 6 patients showed cardiac arrhythmias consisting of ventricular extrasystoles, bradycardias, or nodal rhythm.

The second group consisted of 122 patients in whom trichloroethylene was used with nitrous oxide-oxygen for the second stage of labor, either with or without additional techniques. The following observations were noted:

A. Trichlorethylene-nitrous oxide-oxygen anesthesia alone in 107 cases was associated with arrhythmias in 48 cases (44.8%), consisting primarily of unifocal and multifocal ventricular extrasystoles, bigeminal and nodal rhythms, or bradycardia (Chart 1). These arrhythmias appeared most frequently at the time of maximum dilation of the perineum and disappeared approximately two minutes

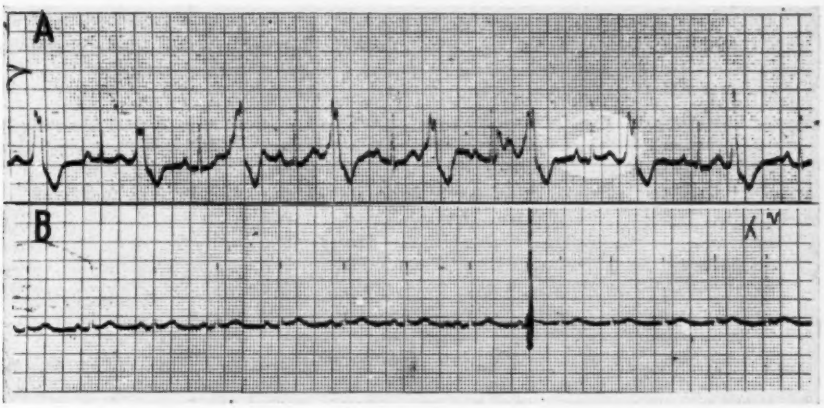


Chart 1.—Common types of trichloroethylene cardiac arrhythmias: *A*, multifocal ventricular extrasystoles and bigeminal rhythm; *B*, nodal rhythm.

later in most cases. Blood pressure changes consisted of mild increases or no change in most cases until the completion of the third stage of labor, at which time the systolic blood pressure usually decreased 10 to 15 points. However, the very occasional presence of severe bradycardia tended to be associated with a moderate hypotension. Intrauterine manipulation did not appear to precipitate cardiac arrhythmias (three cases of manual removal of placenta). The vapor concentrations of trichloroethylene in these cases varied from 0.5 to 0.8% and produced first-plane anesthesia along with the nitrous oxide-oxygen.

B. In 15 cases of trichloroethylene-nitrous oxide-oxygen anesthesia, a pudendal block was also administered. Here also an attempt was made to produce first-plane anesthesia. Only one of these patients showed any disturbance of cardiac rhythm, and this consisted of a single ventricular extrasystole.

C. Atropine (0.4 mg.) was administered intravenously 2 to 10 minutes prior to the administration of trichloroethylene-nitrous oxide-oxygen anesthesia in 33

patients as a prophylactic measure. In these patients the bradycardia seen in the previous cases did not develop, but 12 patients did show either ventricular or nodal arrhythmias. This dose of atropine was not considered sufficient to produce complete vagal blockade.

D. Electrocardiograms taken on a small group of control patients under chloroform anesthesia (20 patients) revealed arrhythmias similar to those of trichloroethylene in 70% (14 patients). Of 10 patients under nitrous oxide-oxygen-ether anesthesia, one showed auricular extrasystoles. Arrhythmias were not recorded in 10 patients under regional anesthesia, in 6 patients under nitrous oxide-oxygen anesthesia, or in 4 patients who had no anesthesia. This work is summarized in Table 1. Interpretation of this material tends to indicate that the initiation of the cardiac arrhythmias which develop under trichloroethylene anesthesia in this group of patients, depends both on concentration of the drug (over 0.5%) and on reflex perineal sensory stimulation. Trichloroethylene-vapor concentrations were determined by use of the interferometer.[9]

The third series consisted of a group of patients undergoing minor gynecological surgery under thiopental (pentothal®) sodium-nitrous oxide-oxygen-trichloro-

TABLE 1.—*Cardiac Arrhythmias During Second Stage of Labor*

	%	No. Patients
Trichloroethylene-nitrous oxide-oxygen	44.8	107
Chloroform	70.0	20
Nitrous oxide-oxygen ether	10.0	10 only
Nitrous oxide-oxygen	0.0	6 only
Regional	0.0	10 only
No anesthesia	0.0	4 only
Trichloroethylene-nitrous oxide-oxygen: regional anesthesia	6.6	15
Trichloroethylene-air	60.0	10

ethylene anesthesia. Of 57 patients, 20, or 35.08%, revealed electrocardiographic abnormalities consisting again of unifocal and multifocal ventricular extrasystoles, nodal rhythm, and bradycardia. In this group, nodal rhythm and bradycardia were frequently seen together and appeared to be related to somewhat higher vapor concentrations of trichloroethylene, that is, above 0.7%. These tended to revert to normal on decreasing the concentration. The ventricular extrasystoles and bigeminy were noted at somewhat lower concentrations (0.5 to 0.7%), and could be reverted to normal by the intravenous administration of procaine amide (Chart 2). Of 25 control patients having similar surgery, premedication (meperidine [demerol®] and hydrochloride and atropine), and anesthesia, except for the absence of trichloroethylene, in 3, or 12%, arrhythmias developed, one of which coincided with a period of rather severe hypoxia associated with laryngospasm.

The fourth series consisted of a group of 325 surgical patients in whom trichloroethylene was used to supplement other anesthetic agents, primarily thiopental sodium, curare, and nitrous oxide. The surgery here was primarily in the region of the head and neck; electrocoagulation was used. In 15 cases, or 4.7%, trichloroethylene was discontinued because of the development of bradycardia, with or without hypo-

9. Hall, K.; Garlington, L.; Stephen, C. R., and Nowill, W. K.: Estimation of Trichlorethylene Vapor Concentrations by Use of the Interferometer, to be published.

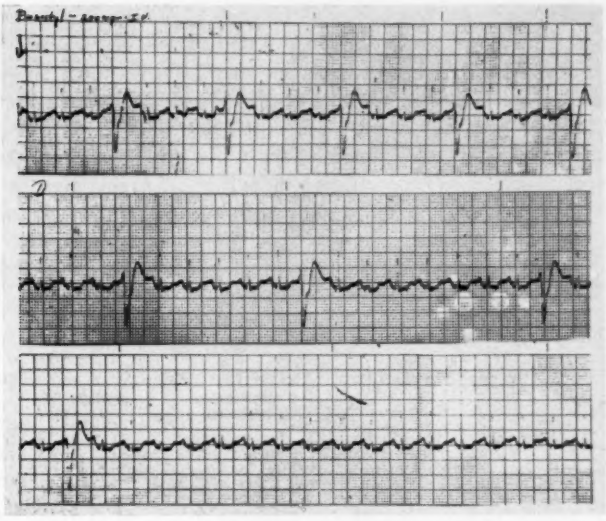


Chart 2.—Patient E. H., aged 41, had dilatation and curettage performed under thiopental sodium-nitrous oxide-oxygen-trichloroethylene anesthesia. Chart shows ventricular extrasystoles, which were reverted to sinus rhythm by intravenous administration of 200 mg. of procaine amide.

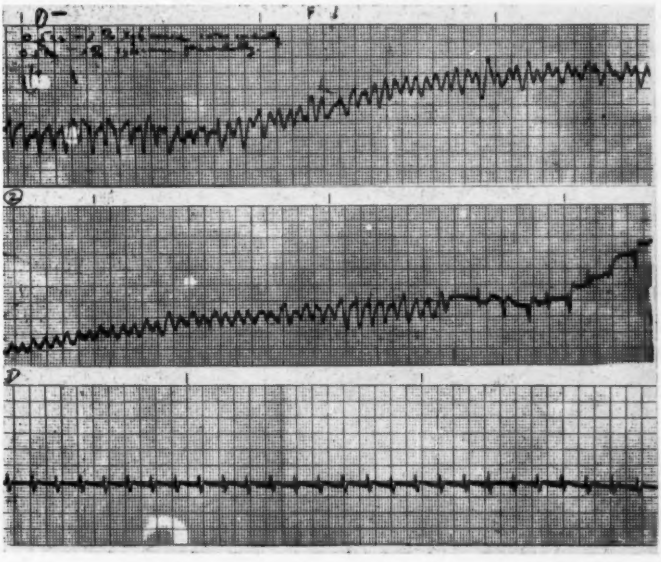


Chart 3.—Ventricular fibrillation to point of marked tachypnea produced in rabbit under intratracheal nitrous oxide-oxygen-trichloroethylene anesthesia. No premedication was given. Ventricular fibrillation was reverted to ventricular tachycardia and sinus rhythm by intracardiac and pericardial injection of 1% lidocaine hydrochloride.

tension (12 cases), or an irregular pulse (3 cases), as noted by palpation. The discontinuance of trichloroethylene and the addition of ether resulted in the disappearance of the abnormality.

Electrocardiographic tracings were taken on two monkeys and five rabbits under trichloroethylene-oxygen anesthesia. These animals were curarized and placed on the Marshall respirator. Trichloroethylene vapor was added with the Foregger vinethene® type vaporizer in concentration up to 3.5%. Arrhythmias were difficult to induce in these animals but did appear with the higher concentrations. The arrhythmias consisted of ventricular extrasystoles, nodal rhythm, and ventricular tachycardia. Ventricular fibrillation was produced in a single rabbit and was reverted to sinus rhythm by intracardiac injection of 1% lidocaine (xylocaine®)

TABLE 2.—*Liver Function in Postpartum Patients*

	Icterus Index		Sulfobromophthalein		Cephalin Flocculation		Thymol Turbidity	
	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal	Normal	Abnormal
Trichloroethylene	30	0	39	5*	29	∓	14	0
Chloroform	..	..	14	6	16	4	..	..
Regional	..	..	9	1†	..	..	10	0
Ether	..	..	12	2	..	..	10	4

* Three patients with normal cephalin flocculation tests; two with known prepartum liver disease.
† Patients with known liver disease.

TABLE 3.—*Renal Function Tests*

Phenolsulfonphthalein Excretion Tests	Normal	Abnormal
Trichloroethylene-nitrous oxide-oxygen	54	8 (Preeclampsia)
Nitrous oxide-oxygen-ether	10	2
Trichloroethylene-air plus regional	15	0
Regional, nitrous oxide, or no anesthesia	23	1 (Preeclampsia)
Blood Creatinine		
Trichloroethylene-nitrous oxide-oxygen	14	0
Postpartum Urinalysis		
Trichloroethylene-nitrous oxide-oxygen	28	2

hydrochloride (Chart 3). In no instance was ventricular tachycardia or fibrillation seen by electrocardiographic tracings or suspected clinically in patients. However, the presence of tachypnea indicates the presence of trichloroethylene-vapor concentrations above 0.5% and well within the range which may produce cardiac arrhythmias.

Liver Function.—An attempt was made to assess the effect of trichloroethylene on liver function as compared with other well-known anesthetic drugs. This work is summarized in Table 2.

Six adult rabbits were anesthetized with 50% nitrous oxide-oxygen-trichloroethylene for periods varying from one to eight hours, with an average of five and one-half hours. Three to seven days later, sulfobromophthalein tests were performed, and these animals were then killed. Gross and microscopic examinations of the liver in these animals revealed no necrosis and the presence of minimal amounts of fat deposits with variable amounts of glycogen. The dye tests were all normal.

The rise in blood glucose level coincident with general anesthesia is thought by many to reflect the relative liver toxicity of general anesthetic agents. Ten obstetric patients had venous blood drawn just prior to induction and again 30 minutes after induction of trichloroethylene-nitrous oxide-oxygen anesthesia. These patients had an average increase in blood glucose of 5 mg. per 100 cc., varying from 0 to 20 mg. per 100 cc. Six adult rabbits were tested similarly, revealing an average increase of 64 mg. per 100 cc.

TABLE 4.—*Arterial Blood pCO_2 Values*

Five Patients Under Thiopental Sodium-Nitrous Oxide-Oxygen-Trichloroethylene Anesthesia

No.	Mm. Hg	
1	41.5	
2	56.0	Interpretation:
3	42.0	No significant change
4	41.4	from normal
5	41.9	

Mean pCO_2 — 44.6

Two Rabbits Under Trichloroethylene-Air Anesthesia to Point of Marked Tachypnea

No.	Before	During
1	26.6	25.1
2	29.0	28.37

TABLE 5.—*pH-Patients Under Thiopental Sodium-Nitrous Oxide-Oxygen-Trichloroethylene Anesthesia*

No.	Before	During Tachypnea
1	7.33	7.24
2	7.37	7.37
3	7.25	7.31
4	7.32	7.32
Mean	7.32	7.31

Total twelve patients during tachypnea—mean pH—7.318
Standard deviation ..... $\mp$ 0.07
Standard error 0.02

Interpretation: No significant change in pH
Mean pH—resting normal subjects unanesthetized 7.37 ± 0.01

Two Rabbits Anesthetized with Trichloroethylene-Air to Point of Marked Tachypnea

No.	Before	During Anesthesia
1	7.33	7.33
2	7.29	7.28

Our general interpretation of these experiments was that trichloroethylene had less adverse effect than either chloroform or ether on liver function.

Effect of Trichloroethylene on Renal Function.—An attempt was also made to assess the effect of trichloroethylene on renal function as compared with other anesthetic agents. This material is summarized in Table 3. The eight patients with abnormal phenolsulfonphthalein tests were preeclamptic and showed no decrease in renal function, as compared with the prepartum state. The kidneys of the previously mentioned six rabbits revealed no pathological evidence of glomerular or tubular damage. This work indicates to us that trichloroethylene has no apparent adverse effect upon renal function.

ACID-BASE BALANCE STUDIES

Johnstone [10] has postulated that the tachypnea seen with trichloroethylene anesthesia is due to bronchospasm and carbon-dioxide retention. We attempted to gather information on this point by obtaining arterial blood carbon-dioxide tension and pH values prior to induction and during thiopental sodium-trichloroethylene-nitrous oxide-oxygen (25 to 40% oxygen) tachypnea on four surgical patients. On an additional eight surgical patients, arterial blood samples were obtained only during the tachypnea. These figures are summarized in Tables 4 and 5 and indicate that neither respiratory acidosis nor hypocapnia was present. It should be mentioned here, however, that these patients were tachypneic for only short periods of time. It is interesting to note that the arterial oxygen saturation of these 12 patients during surgery averaged 97.7%.

In addition, 19 postpartum patients had urine examinations for acetone and diacetic acid. Only one patient had a faintly positive diacetic acid test. We felt then that the metabolic acidosis so frequently seen after ether anesthesia was not present after use of trichloroethylene anesthesia.

CLINICAL IMPRESSIONS

Trichloroethylene has been utilized by us primarily by three techniques. The first of these is trichloroethylene-air mixtures administered with the cyprane, McGill, or Duke inhalers in 140 cases for the production of analgesia for short painful procedures. In these situations no attempt was made to produce full anesthesia and trichloroethylene-vapor concentrations were generally less than 0.5%. These patients usually reacted to the painful stimulus but had excellent amnesia. An important point in the technique of utilizing the inhaler should be noted here. This is, that adequate time must be given for the inhaler to produce analgesia prior to the initiation of the painful stimulus. The analgesia is quite rapid but does require usually 15 to 30 inhalations.

Two examples may be of value to illustrate the versatility of this method. An elderly patient with advanced, widespread, cancer in terminal state was brought to our attention because of severe pain. Morphine in large frequent doses relieved pain temporarily but produced marked respiratory depression (4 or 6 a minute). The cyprane inhaler was suggested and used with excellent pain relief, until the patient died 72 hours later. Another instance was that of a graduate nurse with a ureteral calculus and severe colic. Urologic examination had failed to reveal this calculus. In this patient, generalized urticaria developed from narcotic drugs. The cyprane inhaler was utilized intermittently for 72 hours, at which time the urologic condition subsided. Analgesia and amnesia had been excellent. Postanalgesic liver and kidney function studies (phenolsulfonphthalein and cephalin flocculation tests) were entirely normal.

From January, 1951, through March, 1952, 253 patients on the obstetrical service (Duke University) utilized this technique by self-administration during the first stage of labor. Previously, a similar group of 120 patients (Millard Fillmore Hospital) had been analyzed by one of us (W. K. N.). In the latter series, the amount of analgesia and effect on the progress of labor were evaluated by the obstetrician, obstetrical nurse, and anesthesiologist. Statements concerning the drug were recorded by the obstetrical nurse during the course of labor. In addition, several

10. Johnstone, M.: Pethidine and General Anesthesia, Brit. Med. J. **13**:943, 1951.

days post partum each patient was interrogated as to how much she remembered of her labor and the degree of discomfort of that labor. These results are condensed in Table 6. In general, those patients who had nausea or headache or who disliked the odor, to the extent of refusing to use the inhaler, had a poor analgesic and amnesic effect.

In both groups, the majority of patients were also given meperidine in a total dose of 50 to 200 mg., with or without scopolamine (hyoscine) hydrobromide, or a barbiturate (62 of 120 patients first series and 219 of 253 patients second series) during the course of labor. The larger amounts of meperidine were used early in the series before it was realized that they were unnecessary. Our general impression is that a small dose of meperidine (50 mg.) produces "basal sedation and analgesia," which potentiates the analgesia of trichloroethylene without adverse effect on the fetus.

This use of trichloroethylene appeared to be exceptionally satisfactory. The analgesia and amnesia were excellent. It was found that by utilizing very low con-

TABLE 6.—*One Hundred Twenty Obstetrical Patients During First Stage of Labor (Trichloroethylene Analgesia)*

	No. of Patients
Analgesia	
Good	108
Fair	4
Poor	8
Adverse Effects	
Nausea	3
Headache	5
Dislike of odor	5
Disorientation	2
Amnesia	
Good	89
Fair	23
None	8

centrations of trichloroethylene at first, fewer patients noted nausea or dislike of the odor. The concentrations then could be gradually increased to produce analgesia. Trichloroethylene analgesia may be started at the time when other analgesic agents are usually administered. This varies somewhat with the views of the obstetrician, but in general is when active progressive labor is well established. If begun too early, labor may be temporarily slowed. The inhaler appears to be particularly valuable in cases such as breech presentation when active participation in the expulsive process by the mother is indicated. Our experience is similar to that of Dr. Lewis F. McLean,[11] who has utilized this technique, since 1949, on a large group of obstetrical patients.

The second method is that of trichloroethylene added to nitrous oxide-oxygen anesthesia produced by a McKesson machine. This method has been generally utilized for the second stage of labor in 197 cases and only occasionally for surgical procedures of short duration. The induction of anesthesia is smooth and very rapid, without evidence of irritation to the upper respiratory tract. Nausea and emesis during induction is rare (0.5%). Anesthesia is maintained in a light plane in which

11. McLean, L. F.: Personal communication to the authors.

the eyeballs are moving and the laryngeal reflexes present. The level of anesthesia may be varied with ease so that, if desired, anesthesia may be lightened to allow the mother to push with contractions. In low or outlet forceps deliveries, usually all anesthesia is discontinued and 100% oxygen administered at the time of satisfactory application of forceps. In many cases, the mother is awake but drowsy at the time of forceps extraction of the baby. The anesthetic is then readministered when required for repair of the episiotomy. Muscular relaxation is absent. Because of this lack of muscular relaxation, this type of anesthesia is not satisfactory for version and extraction. Emergence is smooth with only occasional emesis, which usually occurs after nearly complete awakening. Maternal complications appear to be nearly absent (Table 7). This, however, is not true if hypoxia is induced by allowing too great

TABLE 7.—*Maternal Complications of Anesthesia, 1,800 Cases*

			No.	%
Postpartum emesis				
Ether			78	18.4 (Aspiration of emesis and death—1)
Nitrous oxide-oxygen			10	1.8
"Trilene"			9	2.0
Regional			7	2.3
Hypotension	1	Spinal (hypotension due to blood loss not included)		
Bronchospasm	1	Trichloroethylene		
Laryngospasm	5	Ether		

TABLE 8.—*Infants Requiring Resuscitation, 1,800 Cases*

			No.	%
Ether			17	4.0
Nitrous oxide-oxygen			5	1.1
Trichloroethylene			13	3.0
Trichloroethylene-nitrous oxide-oxygen	6	3.0		
Trichloroethylene-air	4	3.1		
Trichloroethylene-regional	3	2.7		
Regional			7	2.3
Regional and nitrous oxide-oxygen			3	3.0

a concentration of nitrous oxide to exist. In all cases of this series, oxygen concentrations of the inspired mixture varied from 25 to 50%. We have noted one asthmatic patient under this type of anesthesia who had a period of severe bronchospasm which was relieved by transferring the anesthetic to ether.

The effect on the newborn may be noted by referring to Table 8. The percentage of babies needing resuscitation was less than with ether but more than with regional or nitrous oxide anesthesia alone. These figures, however, need some elucidation. In this hospital, nitrous oxide is never administered with less than 20% oxygen, so that it is usually used for patients of high parity and easy, short, spontaneous deliveries. Also we noted that doses of meperidine greater than 50 mg. in the four hours preceding terminal labor combined with any general anesthesia tended to produce babies slow to react. These figures are not corrected for obstetrical complications.

Our clinical impression is that babies delivered under the combination of pudendal block and trichloroethylene-air analgesia breathe and cry more readily than those delivered under nitrous oxide-oxygen-trichloroethylene.

If the terminal trichloroethylene-air or trichloroethylene-nitrous oxide-oxygen anesthesia was prolonged for 15 minutes or more prior to delivery, babies occasionally tended to be "analgesic," in that their eyes were open, and extremities moving, but sometimes they did not cry or breathe immediately, even with skin stimulation. If immediate resuscitation (pharyngeal suction and oxygen inflation of lungs) was employed, no adverse effects were noted and spontaneous breathing and crying would occur in two to three minutes. However, if they were allowed to become severely hypoxic before instituting resuscitation procedures, then the return was much slower. There were no neonatal deaths in which trichloroethylene appeared to be instrumental.

The third method is that of trichloroethylene supplementation of other general anesthetic drugs, as mentioned previously. It is particularly useful in situations in which explosive anesthetic agents are contraindicated. Approximately 75% of these cases have been from the plastic surgery service. Our impression was that smaller amounts of thiopental or thiamylal (surital®) sodium were required and that patients reacted after surgery quicker and with much less nausea and emesis.

We have seen no evidence of central nervous system or cranial or peripheral nerve injury from our use of trichloroethylene.

SUMMARY AND CONCLUSIONS

An attempt has been made to analyze the drug trichloroethylene from the standpoint of possible abnormalities in physiology induced by this drug and its clinical usefulness in 1,032 patients. Experimental animals were also utilized in this study.

We feel justified in making the following conclusions:

1. Trichloroethylene produces no apparent adverse effect on renal or hepatic function or structure.

2. In vapor concentrations below 0.5%, trichloroethylene produces little or no abnormality in cardiac rhythmicity, while in concentrations above 0.5%, cardiac arrhythmias consisting of unifocal and multifocal ventricular extrasystoles, bigeminal and nodal rhythms, and simple sinus bradycardias may be seen. These arrhythmias are infrequently apparent clinically and only occasionally produce a decrease in systemic blood pressure. There were no deaths during anesthesia and none in the postanesthetic state which were related to the drug. While these arrhythmias resemble those seen with chloroform and cyclopropane, no instance of serious cardiac dysfunction has been noted by us. Safe levels of trichloroethylene appear to be 0.5% vapor concentration or less. This is below the level producing tachypnea. Tachypnea is a definite indication of excessive trichloroethylene-vapor concentration.

3. Trichloroethylene does not appear to induce either respiratory or metabolic acidosis.

4. Trichloroethylene appears to increase cerebral blood flow moderately.

5. Analgesia with trichloroethylene-air for the first stage of labor and for short painful procedures appears to be satisfactory and useful. This method, either alone or combined with regional anesthesia, may be used successfully for terminal labor. Transient and intermittent self-administration by the patient of vapor concentrations of trichloroethylene above 0.5% may be safe, since the patient releases the mask as soon as unconsciousness is attained. High blood levels are thereby prevented. Amnesia appears to be excellent. The newborn are not depressed unless higher con-

centrations are utilized continuously for more than 15 minutes or combined with the larger amounts of narcotic or sedative drugs. Combined with nitrous oxide-oxygen, trichloroethylene appears to produce successful light general anesthesia for terminal labor.

6. As a supplemental agent, trichloroethylene may successfully be combined with the thiobarbiturates, nitrous oxide, and muscle relaxant drugs.

7. We should like to inject a word of warning here concerning the use of this drug. Trichloroethylene is an analgesic agent and should be used for that purpose. We feel that to use it as a primary anesthetic drug will result in vapor concentrations and therefore blood concentrations which are dangerous. It should be utilized to produce analgesia in a conscious patient or to supplement other anesthetic drugs.

St. Luke's Hospital, Chicago (Dr. Searles).

ABSTRACT OF DISCUSSION

DR. CHARLES M. BARBOUR, Hartford, Conn.: Drs. Nowill, Stephen, and Searles are to be commended for the excellence of their thorough investigation and evaluation of trichloroethylene and for rendering this conservative report. In recommending that the use of trichloroethylene be limited to production of analgesia or as a supplementary agent to be used in combination with other anesthetic agents, they have established a safe precedent.

The authors' objectives of the evaluation of trichloroethylene, with reference to its potential to alter physiologic processes and its potential for hazard in clinical use, have been achieved. In establishment of the use of trichloroethylene as a safe procedure only when used in concentrations of 0.5% or less, indications for its employment have been clearly defined. In addition, their investigations have again reminded us that regional and combined anesthetic procedures alter physiologic processes least of all.

Because of its untoward effects on the cardiorespiratory system and in the absence of such complete scientific data, many anesthesiologists have restricted the use of trichloroethylene to the production of analgesia for obstetric patients and for performance of minor surgical procedures. It is gratifying to those of us who have noted these clinical observations to have this clinical impression substantiated. This investigation and evaluation together with the clinical experience of others (Dr. D. M. Little, of New Haven, Conn.) prompts us to employ this agent for production of analgesia during the performance of neurosurgical procedures.

One of the hazards of administration of analgesic and anesthetic agents to obstetric patients is encountered when food has been ingested within one to six hours prior to onset of labor. I should like to ask Dr. Nowill if he considers this to be a contraindication to autoadministration of trichloroethylene when regional techniques, including spinal anesthesia, cannot be employed?

The effectiveness of solutions of procaine hydrochloride and procaine amide in the prevention of cardiac arrhythmias warrants additional comment. Have you investigated the effectiveness of the intravenous administration of these drugs as prophylactic measures when employed prior to and during the administration of trichloroethylene?

DR. SCOTT M. SMITH, Salt Lake City, Utah: I think certainly Dr. Nowill and the group are to be complimented upon their efforts to give a sincere and true evaluation of another anesthetic agent. Dr. Nowill has adequately pointed out to us the hazards which may be present if this agent is pushed beyond use as an analgesic agent.

You notice, since the cardiac irregularities were absent in concentrations below 0.5 or 0.6%, the use in obstetrics perhaps, as pointed out, may be a very valuable place for this drug.

I should like to have more information on the use of atropine in attempting to prevent the cardiac irregularities which occur with the higher concentrations; I should like to know, Dr. Nowill, something about the dosage of atropine used in attempting to establish blockade.

I should also like to know if the cardiac irregularities pertaining to higher concentrations are to be considered seriously.

DR. NOWILL, Durham, N. C.: The first question asked was about a full stomach. We feel that, in general, any patient with a full stomach should not be given any drug which puts him to sleep. However, analgesia with trichloroethylene for obstetrical use may be accomplished

without complete unconsciousness. If the obstetrical procedure requires full anesthesia and the patient has a full stomach, a condition of which the anesthetist is unaware (which, of course, occurs frequently in obstetrical work and is responsible for part of maternal mortality), the technique of nitrous oxide-oxygen-trichloroethylene appears to provide somewhat greater safety than other general anesthetic techniques. Patients under this technique either do not have emesis, or it appears to occur after they have completely reacted. However, this complication should be anticipated and aspiration prevented.

As to the second question about procaine hydrochloride and procaine amide for prophylaxis of cardiac arrhythmias, we have used the latter drug in only a small group of patients and at present feel that it is probably better to use lower concentrations of trichloroethylene. Concentrations of 0.5% or lower appear to produce arrhythmias infrequently. Concentrations of 0.5 to 1% seem to be associated rather frequently with arrhythmias, but these arrhythmias appear to have little adverse effect on cardiovascular dynamics. The cardiac rhythm may be readily reverted to normal by lowering the concentration of trichloroethylene. We have used very high concentrations of trichloroethylene (3%) only in animals in which it is possible to produce ventricular tachycardia and fibrillation.

As far as atropine is concerned, we have used both atropine and methantheline (banthine®) bromide, the atropine in a 0.4 mg. dose. This amount of atropine does not produce complete vagal blockade but does prevent bradycardia.

We feel that this drug is safe to use if it is not used in high concentrations, which means that we cannot try to do everything with it. Analgesia can be produced, and other anesthetic agents can be supplemented, but trichloroethylene should not be used as a primary anesthetic agent.

NEW TECHNIQUE OF SURGICAL MANAGEMENT OF THE PATENT DUCTUS ARTERIOSUS

HARRY A. DAVIS, M.D.
LOS ANGELES

TECHNICAL difficulties which are encountered during surgical operations for patent ductus arteriosus arise directly or indirectly from dissection of the ductus. In children the ductus is relatively long and has a small lumen. In adults, however, it is often short, has a large lumen, and may therefore be difficult to isolate. The danger is increased if the ductus is friable or is surrounded by adhesions. Dissection of the posterior wall is particularly likely to tear the ductus and cause hemorrhage. Whether the procedure contemplated is division of the ductus, as Gross [1] advocates (Fig. 1), or ligation by the Blalock [2] method (Fig. 1), the ductus

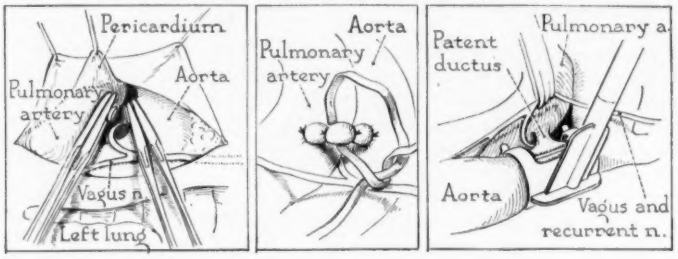


Fig. 1.—Methods of treating the patent ductus arteriosus: right, Freeman, Leeds, and Gardner: center, Blalock; left, Gross.

must first be carefully dissected out. If it has a large lumen, even the procedure of ligation may result in tearing of the wall when the ligature is drawn tight.

Hemorrhage, which occurs during operations for the patent ductus arteriosus, may be due not only to a tear in the wall of the ductus (most frequent), but also to a tear in the ductus at its junction with the aorta, or to tearing of the pulmonary artery near or at its junction with the ductus. An analysis of these unfortunate mishaps reveals that they are basically the result of a lack of adequate control of the two vessels connected with the patent ductus arteriosus, namely the aorta and the

From the Department of Surgery, College of Medical Evangelists, Los Angeles Division.

1. Gross, R. E.: Complete Surgical Division of the Patent Ductus Arteriosus: A Report of 14 Successful Cases, Surg., Gynec. & Obst. **78**:36-43 (Jan.) 1944.

2. Blalock, A.: Operative Closure of the Patent Ductus Arteriosus, Surg., Gynec. & Obst. **82**:113-114 (Feb.) 1946.

pulmonary artery. Potts-Smith aortic forceps has been employed [3] to prevent hemorrhage from the aortic end of the ductus (Fig. 1). This, however, leaves the pulmonary artery uncontrolled.

Recent studies [4] have demonstrated that the lung is very resistant to ischemia produced by occlusion of the pulmonary artery. Temporary occlusion of the pulmonary artery in monkeys (Macacus rhesus) for periods up to 48 hours did not cause irreversible changes in the structure of the ipsilateral lung. The studies to be reported in the present paper were designed to determine if simultaneous total occlusion of the left pulmonary artery and partial occlusion of the aorta could be performed during the operative closure of the patent ductus arteriosus. Preliminary investigations had suggested that such a procedure might be technically feasible.[5]

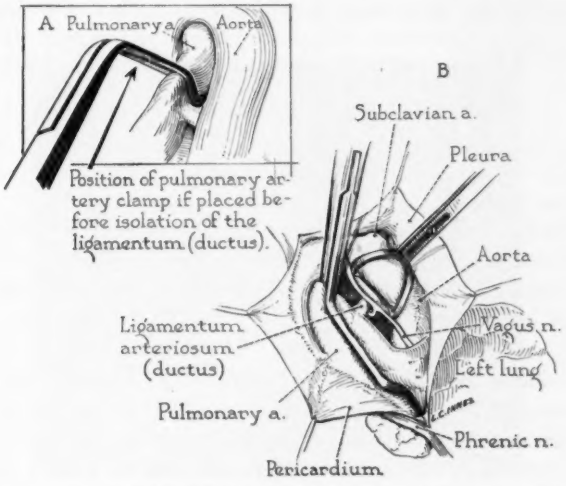


Fig. 2.—Technique of division employing simultaneous occlusion of the pulmonary artery and aorta: *A*, pulmonary artery forceps placed before isolation of ligamentum (ductus); *B*, pulmonary artery forceps placed after isolation of ligamentum (ductus).

EXPERIMENTAL STUDIES

Dogs weighing from 25 to 35 lb. (11.34 to 15.88 kg.) were anesthetized with ether-oxygen administered by an automatic respirator (Burns valve) through an intratracheal tube. The chest was opened through a left posterolateral incision, and the fifth rib was resected. The pericardium was opened between the left phrenic and left vagus nerves and was divided down to and over the left pulmonary artery. The incision in the pericardium was continued over the parietal pleura covering the aortic arch. The aortic arch was then mobilized and partially occluded with aortic

3. Freeman, N. E.; Leeds, F. H., and Gardner, R. E.: Technique for Division and Suture of Patent Ductus Arteriosus in Older Age Group, Surgery **26**:103-108 (July) 1949.

4. Davis, H. A.; Gordon, W. B.; Hayes, E. W., Jr., and Wasley, M. T.: Effects upon the Lung of Varying Periods of Temporary Occlusion of the Pulmonary Artery, A. M. A. Arch. Surg. **64**:464-474 (April) 1952.

5. Davis, H. A.: A Method of Surgical Management of the Difficult Patent Ductus Arteriosus: A Preliminary Experimental Study, M. Arts & Sc. **6**:9 (Jan.-Mar.) 1952.

forceps (Blalock modification of the Potts-Smith forceps) in the region of the ligamentum arteriosum. The subpleural areolar tissue lying on the surface between the aorta and the pulmonary artery above the ligamentum arteriosum was carefully removed. The two vessels could be easily separated by finger dissection.

In one group of animals the ligamentum arteriosum was dissected out and mobilized before noncrushing forceps were applied to the left pulmonary artery above the ligamentum (Fig. 2*B*). In a second group of animals noncrushing forceps were applied to the left pulmonary artery before the ligamentum arteriosum was isolated (Fig. 2*A*). The ligamentum arteriosum was then exposed and divided. In earlier studies a noncrushing clamp was placed on the left pulmonary artery below the ligamentum to prevent retrograde reflux of blood from the lung. Later, this was found to be unnecessary. Each end of the divided ligamentum was sutured with 00000 nonabsorbable surgical (silk) suture material or ligated. Care was taken to avoid injuring the recurrent branch of the left vagus nerve. The pulmonary artery forceps were removed followed by the aortic forceps. The pericardial sac was left open. The lung was inflated and the chest closed in the usual manner without drainage. Dogs which were subjected to this procedure have shown no ill effects, and all have survived up to the present. The period of occlusion of the pulmonary artery was relatively short, ranging from 15 to 30 minutes. This is well below the tolerance level of 48 hours established by our experiments in monkeys (Macacus rhesus).[4]

ANATOMY OF THE PULMONOAORTIC JUNCTION

Anatomic dissections were performed in the human cadaver to determine if a sufficient length of pulmonary artery was normally present above the ductus arteriosus to permit application of occlusive forceps. It was necessary to consider three points: (1) the problem of exposure of the left pulmonary artery above the ductus; (2) the ease of separation of the left pulmonary artery from the arch of the aorta, and (3) the approximate length of the left pulmonary artery between the point of bifurcation of the main pulmonary artery and the ligamentum (or ductus) arteriosum.

The anatomic approach used to expose the left pulmonary artery in dogs was found to be equally effective in the human cadaver. The pericardial sac was opened between the left vagus and left phrenic nerves, and the line of incision in the pericardium was continued so as to open the parietal pleura covering the aorta. The left pulmonary artery was partly covered by a reflection of the pericardial sac and partly by parietal pleura. A variable amount of fat beneath the pleura was removed to enhance exposure of the pulmonoaortic junction. The left pulmonary artery above the ligamentum arteriosum was easily separated from the aorta by finger dissection. This permitted the left pulmonary artery, the bifurcation of the main pulmonary artery, and a portion of the right pulmonary artery to be readily visualized. The approximate length of the left pulmonary artery between the bifurcation of the main pulmonary artery and the ligamentum arteriosum was 2 in. (5 cm.). In the human cadaver the left pulmonary artery above the ligamentum arteriosum could be readily occluded with noncrushing forceps without diminishing the lumen of the main pulmonary artery.

DESCRIPTION OF PULMONARY ARTERY FORCEPS

Difficulties were encountered in adapting the vascular forceps, which are at present available, to occlusion of the left pulmonary artery proximal to the ligamentum (ductus) arteriosum. It was necessary to have a noncrushing forceps with

blades sufficiently long to occlude, if required, the lumen of an enlarged adult pulmonary artery. Because of the depth of the artery within the chest, it was advisable to have an instrument the curves of which could fit those of the open chest. Finally, the instrument had to be light in weight to prevent any drag on the main pulmonary artery. Accordingly, an instrument [6] embodying these features was devised and is illustrated (Fig. 3). It has been found, incidentally, that the forceps, because of their construction, have certain advantages when used to clamp the auricular appendage during the performance of mitral commissurotomy and the inferior vena cava during portacaval anastomosis.

COMMENT

These results indicate that it is possible to occlude the left pulmonary artery and the aorta simultaneously during division of the ligamentum arteriosum. The resist-

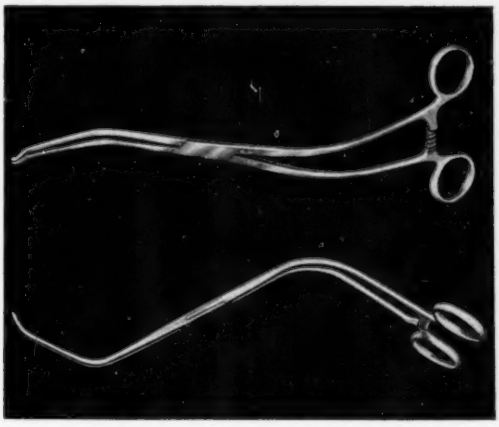


Fig. 3.—Pulmonary artery forceps.

ance of the lung to the ischemia produced by occlusion of the pulmonary artery has already been discussed. This tolerance to ischemia is greater than that possessed by many other tissues, notably the central nervous system, the liver, the heart, the kidneys, and the alimentary tube. Our results in monkeys [4] have been corroborated by subsequent workers [7] who used dogs.

The mechanisms underlying the relative insensitivity of pulmonary tissue to ischemic anoxia are not known but may include the following: 1. The pulmonary tissue has become adapted to a lower oxygen supply. The blood in the pulmonary artery has a relatively low oxygen content and tension. 2. When the pulmonary arterial blood flow to a lung is arrested, the alveolar epithelium and capillary

6. Manufactured by George P. Pilling and Son Company, Philadelphia 4.

7. Blades, B.; Beattie, E. J., Jr.; Hill, R. P., and Thistlethwaite, R.: Ischemia of the Lung, Ann. Surg. **136**:56-62 (July) 1952.

endothelium may receive adequate amounts of oxygen by diffusion from the air present in the alveoli. It has been pointed out that the capillary endothelium in the alveoli depends to a great degree on the alveolar air for its oxygen supply.[8]

SUMMARY AND CONCLUSIONS

A new technique of surgical management of the patent ductus arteriosus is presented. This is based on experimental investigations in lower animals and on anatomic studies in the human cadaver. In the procedure herein described the danger of hemorrhage from accidental tearing of the ductus arteriosus is eliminated by preliminary simultaneous occlusion of the left pulmonary artery and of the aorta. New forceps have been devised for occlusion of the pulmonary artery and are illustrated in the paper.

8. Drinker, C. K.: Pulmonary Edema and Inflammation: An Analysis of Processes Involved in the Formation and Removal of Pulmonary Transudates and Exudates, Monographs in Medicine and Public Health, No. 7, Cambridge, Mass., Harvard University Press, 1945.

DIAPHRAGM PUMP FOR ARTIFICIAL CIRCULATION, TYSON-BOWMAN PUMP

JAMES L. SOUTHWORTH, M.D.
E. CONVERSE PEIRCE II., M.D.
BALTIMORE
THOMAS TYSON
RICHMOND, VA.
AND
ROBERT L. BOWMAN, M.D.
BETHESDA, MD.

IN THE past several years a number of investigators interested in intracardiac surgery have produced pumps to serve as mechanical hearts. Much of this work has been stimulated by the efforts of Gibbon,[1] Dennis and associates,[2] and others to produce an artificial heart-lung system and by the studies of Sewell and Glenn,[3] and others,[4] in which a pump is used to bypass parts of the heart. We became interested in this field in 1949, and thought that a small compact pump could be produced by using the diaphragm principle. This report describes the resulting pump

From the Section on Technical Development, National Heart Institute (Dr. Bowman).

Mr. Tyson is with Experiment Incorporated, Richmond, Va., the builders of this pump.

This work was done in association with the Section of Medicine and Experimental Therapeutics, National Heart Institute, in the Cardiovascular Clinic, Public Health Service Hospital, Baltimore (Drs. Southworth and Peirce).

1. Gibbon, J. H., Jr.: Artificial Maintenance of Circulation During Experimental Occlusion of Pulmonary Artery, Arch. Surg. **34**:1105, 1937. Miller, B. J.; Gibbon, J. H., Jr., and Gibbon, M. H.: Recent Advances in the Development of a Mechanical Heart and Lung Apparatus, Ann. Surg. **134**:694, 1951.

2. Dennis, C.; Spreng, D. S., Jr.; Nelson, G. E.; Karlson, K. E.; Nelson, R. M.; Thomas, J. V.; Eder, W. P., and Varco, R. L.: Development of a Pump-Oxygenator to Replace the Heart and Lungs: An Apparatus Applicable to Human Patients and Application to One Case, Ann. Surg. **134**:709, 1951.

3. Sewell, W. H., Jr., and Glenn, W. W. L.: Experimental Cardiac Surgery: I. Observation on the Action of a Pump Designed to Shunt the Venous Blood Past the Right Heart Directly into the Pulmonary Artery, Surgery **28**:474, 1950; Experimental Cardiac Surgery: II. Further Observation on the Development of a Perfusion Pump for the Purpose of Shunting the Venous Return Directly into the Pulmonary Artery; abstracted, Surgical Forum: Proceedings of the Forum Sessions, Thirty-Sixth Clinical Congress of the American College of Surgeons, Boston, October, 1950, Philadelphia, W. B. Saunders Company, 1951, p. 265.

4. Kantrowitz, A., and Kantrowitz, A.: Experimental Artificial Left Heart to Permit Surgical Exposure of Mitral Valve in Cats, Proc. Soc. Exper. Biol. & Med. **74**:193, 1950. Clowes, G. H. A., Jr.: Experimental Procedures for Entry into the Left Heart to Expose the Mitral Valve, Ann. Surg. **134**:957, 1951.

and indicates how it operates when used to duplicate the right heart bypass operation described by Sewell and Glenn.[3] Additional experience with this pump when used to bypass the left heart is reported elsewhere.[5]

GENERAL REQUIREMENTS FOR A MECHANICAL HEART

The mechanical heart used in these experiments was designed by T. Tyson, guided by the suggestions of Dr. Robert L. Bowman.

It is generally considered that a mechanical heart is essentially a blood pump. As such, it differs from most pumps in that the fluid to be handled is actually a suspension of very fragile particles which must not be crushed by the working parts of the pump nor subjected to excessive impact. It is desirable that the pump be readily sterilized, preferably in the assembled state, and its operation be not inhibited by the chemical action of the blood or by the existence of the solid material in the blood. Some authorities feel that pulsating delivery is desirable to maintain vascular tone. Guided by these basic specifications, existing types of pumps were examined for feasibility as blood pumps.

Conventional fluid pumps of the purely mechanical class (i. e., reciprocating piston, positive displacement rotary, vane pumps, gear pumps, etc.) are not considered satisfactory because of the existence of close-clearance relative moving parts in the pumping chamber which subject the blood-formed elements to considerable crushing. In addition, the sterilization problem with such clearances becomes acute, oftentimes necessitating disassembly. Finally, the accumulation of blood-formed elements and proteins in these clearances may readily cause jamming of the pump.

A number of laboratory-type pumps have been adapted as mechanical hearts, the general trend being to employ the principle of squeezing rubber tubing by rollers, fingers, air pressure, or other means. All these pumps have the fault in common that their action generally subjects the blood to crushing to a greater or less degree. In addition, the drive mechanism is usually complicated and the capacity low, necessitating operation at rather high pulse rates. A redeeming feature of these pumps is their ease of cleaning and sterilizing.

Flexible diaphragm pumps offer a number of advantages as mechanical hearts. They are similar in operation to reciprocating piston pumps, except that the piston is replaced by a flexible diaphragm. Close clearances between moving parts are entirely eliminated, and the pump may readily be cleaned and sterilized. Furthermore, the pump has a relatively great output for the space occupied and will deliver high flows at normal pulse rates. The drive mechanism is comparatively simple and may readily be adapted to various pressure-wave forms. This type of pump was therefore selected as the most promising design to study.[6]

TYSON-BOWMAN HEART PUMP DESIGN

The final configuration, adopted on the basis of the preceding account, is shown schematically in Figure 1. The pump consists of a cylindrical chamber, the lower end of which is a flexible diaphragm attached to the chamber at its periphery and

5. Peirce, E. C., II, and Southworth, J. L.: Pump Circuit for Experimental Intracardiac Surgery of the Left Heart, Arch. Surg., to be published.

6. Since our pump was developed, our attention has been directed to a similar pump. See André-Thomas, J., and Beaudouin, P.: Caractéristiques physiologiques du cœur-poumon artificial pour la perfusion au sang du corps humain, J. Physiologie **43**:311, 1951.

to a piston centrally. The space above the diaphragm is the actual pump chamber, while that below is an air space and does not enter into the function of the pump. Blood arrives from the animal via suitable tubing and enters the pump chamber through the inlet valve, which opens in response to a downward motion of the diaphragm. Blood is returned to the animal through the outlet valve in response to upward motion of the diaphragm. A bubble trap is incorporated at the outlet valve to assist in clearing the system of air. The diaphragm and its piston are driven by a linkage, consisting of a pump rod, bell crank, follower roller, cam, and return spring. The cam is attached to a variable-speed power source.

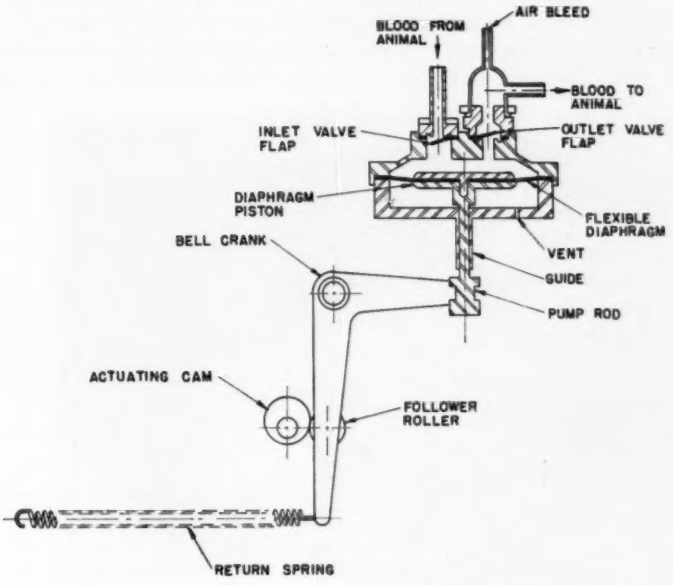


Fig. 1.—Schematic diagram of Tyson-Bowman pump.

MECHANICAL DETAILS AND OPERATION

In operation, the cam, acting through the bell crank, etc., forces the diaphragm upward to discharge the pump chamber. The return of the diaphragm (and the refilling of the pump chamber) is dependent on the return spring, also acting through the bell crank. An increase of spring tension increases the interval during which the diaphragm is drawn downward and consequently may be used as a means of regulating the quantity of blood drawn into the chamber in each cycle of the pump. Maximum pump output for any fixed pulse rate is reached when the spring tension is sufficient to hold the follower roller against the cam throughout the cycle. If desired, the contour of the cam may be modified to obtain a wide variation of pulse pressure-wave forms.

The drive mechanism of the mechanical heart is assembled within a metal cabinet, while the pump unit is mounted on brackets on the front panel.

A Graham variable-speed drive with attached electric motor, having an output speed of 0 to 180 rpm, proved to be satisfactory for present purposes. The cam used to actuate the pump is mounted directly on the output shaft of the drive. The vertical leg of the bell crank, along with the follower cam and return spring, are enclosed, while the horizontal leg of the bell crank projects through the front panel of the cabinet to engage the pump rod. Controls for speed, return spring tension (i. e., pump output) off-on control switch and pilot light (to show when current is on) are mounted on the panel along with the pump unit. The complete mechanical heart is shown in Figure 2. The pump is attached to the bracket on the front panel by means of three knurled screws, which, along with three similar, but shorter, screws, also hold the chamber assembly together. The pump rod is attached to the end of the horizontal leg of the bell crank by means of a yoke, collar, and nut. By removing the attaching screws and this nut, the pump assembly may be removed as a complete unit. The removal of the assembly is shown in Figure 3. As such,

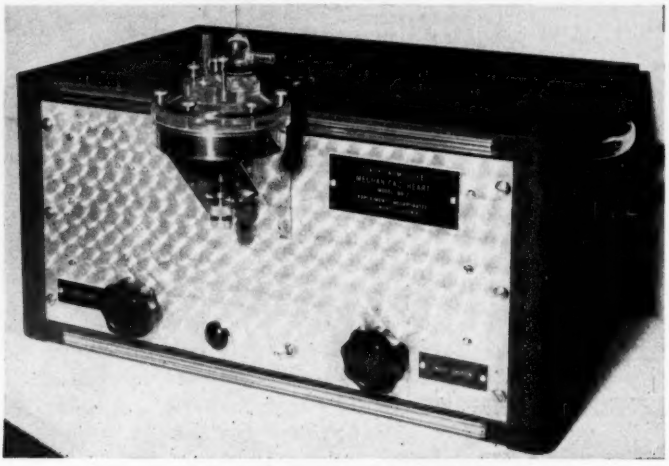


Fig. 2.—Complete unit assembled.

the pump unit may be cleaned and sterilized without further disassembly. Complete disassembly of the pump chamber is possible by removal of the three short screws. Access to the valves is obtained by removal of two knurled nuts on each valve body, which may be accomplished without disturbing other portions of the pump.

To avoid clotting and precipitation of formed blood elements, smoothly finished inert materials are used throughout the pump. Lucite® was selected for the pump body and valve seats, permitting observation of the pump diaphragm and valve flaps. The latter were first made of rubber; however, experience indicated a vinyl plastic material to be superior for this use. Highly stressed parts, such as the pump piston, pump rod, fastenings, etc., are fabricated of stainless steel. An enlarged view of the above components is given in Figure 4.

The pump has a capacity of 4,400 cc. per minute over a range of 50 to 140 pulses per minute at a delivery pressure of 200 mm. Hg. The complete unit measures 22 in. (55 cm.) wide, 20 in. (50 cm.) deep, and 12 in. (30 cm.) high, and weighs approximately 40 lb. (18 kg.).

The unit is sterilized by pumping it full of 1:1000 aqueous benzalkonium (zephiran®) chloride 24 hours prior to use, since in this model parts of the pump are of thermolabile plastic. There is no reason why subsequent models cannot be made to withstand steam sterilization. To date, sterilization with benzalkonium has been satisfactory, however.

EXPERIENCES WITH THE TYSON-BOWMAN PUMP IN BYPASSING THE RIGHT HEART

Eight dogs were used. These varied in weight from 15 to 20 kg. They were anesthetized with pentobarbital sodium; artificial ventilation was maintained with an alternating positive pressure respirator. The right chest was opened; the venae cavae were cannulated with a Leeds[7] cannula through the azygos vein (brass, 0.6 mm., outside diameter), which was in turn connected to the pump intake arm with "tygon" (flexible plastic) tubing (0.5 mm., inside diameter). Outflow for the pump was led to a large branch of the right pulmonary artery. With this arrange-

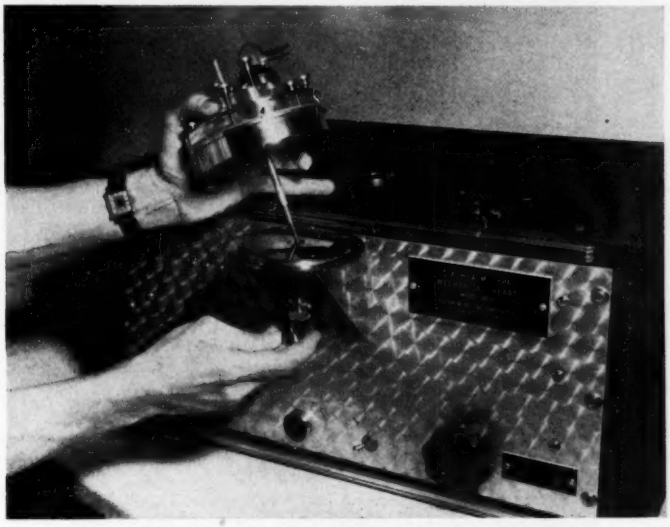


Fig. 3.—Method of removing the pump proper from its actuating mechanism.

ment the right atrium was rendered bloodless except for the rather considerable coronary return. It was possible to open the right atrium, however, without undue blood loss as the coronary return continued to be removed by the heart itself; under these conditions no evidence of air embolism was detected.

Of eight animals, six survived three months or more. One died during operation of ventricular fibrillation and one later, of hemorrhage because of inadequte reversal of heparin effect. The duration of shunting procedures was from 20 to 45 minutes. There was no difficulty in maintaining systemic blood pressure during the period of bypassing the right heart; mean pressures in the eight experiments were as follows: 98, 110, 125, 135, 105, 112, 122, and 90. Figure 5 shows blood pressure tracings from the pulmonary artery and from the aorta recorded simultaneously with strain gauges.

7. Leeds, S. E.: Cannula for Simultaneous Drainage of Both Cavae in Artificial Heart Experiments, Proc. Soc. Exper. Biol. & Med. **75**:468, 1950.

Hemolysis was not excessive. Free plasma hemochromagen was measured before and after operation in five of eight experiments: 52, 72; 4, 20; 4, 12; 6, 36, and 4, 24—all values are expressed in milligrams per 100 cc. of plasma (measured by the method of Hunter and others [8]). Similar results were obtained in the left heart bypass procedures.

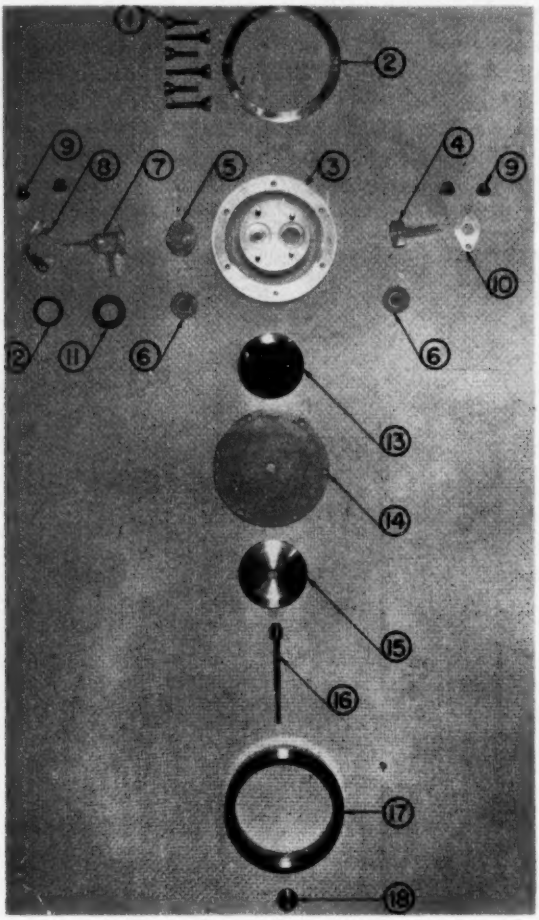


Fig. 4.—Enlarged view of the parts of the pump proper: *1*, pump body retainer screws; *2*, pump body retainer ring; *3*, pump body; *4*, inlet valve tube and seat; *5*, outlet valve seat; *6*, valve flap; *7*, bubble trap; *8*, outlet valve seat and bubble trap yoke; *9*, valve retaining knurled nuts; *10*, inlet valve seat yoke; *11*, bubble trap gasket; *12*, bubble trap pad; *13*, upper half of piston; *14*, flexible diaphragm; *15*, lower half of piston; *16*, pump rod; *17*, pump mount ring; *18*, pump rod nut.

As has been mentioned, the pump is capable of high rates of flow, but the flow actually delivered in these experiments is known only approximately. The pumping

8. Hunter, F. T.; Grove-Rasmussen, M., and Soutter, L.: A Spectrophotometric Method for Quantitating Hemoglobin in Plasma of Serum, Am. J. Clin. Path. **20**:429, 1950.

rate and flow were set empirically by observing the action of the pump prior to tying down the ligatures about the venae cavae; consequently, the great veins appeared to empty but not collapse. If necessary, additional adjustments were made after the ligatures had been tied down. The setting was then left alone during the experiment, and at its conclusion water was pumped through the pump and the output measured for several successive 15-second periods. The approximation of flows thus obtained were 1,800, 2,200, and 2,900 ml. per minute in three experiments.

Technical difficulties due to the pump design were infrequent. The first experiment in which the pump was used went off perfectly. It was found that care must be taken to keep the piston (*16*, Fig. 4) oiled properly to prevent stalling at maximum capacity. When the bore of the inflow and outflow ports was increased from 5 to 8 mm., it was found that the rubber flap valves (*6*, Fig. 4) originally provided tended to prolapse. This was corrected by substituting valves cut from 0.038 in. vinyl sheet; these function perfectly. The rubber diaphragm originally used was found to be quite serviceable and did not leak when properly seated, one having been

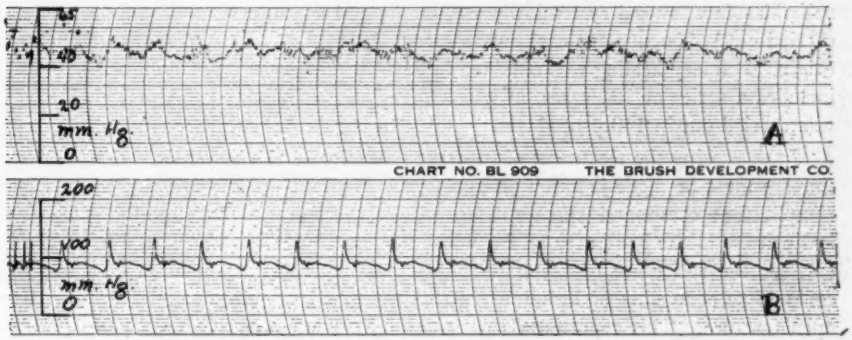


Fig. 5.—Blood pressure tracings during right heart bypass operation, using Tyson-Bowman pump: *A*, from a branch of right pulmonary artery about 1 cm. proximal to point of delivery of output of pump; *B*, from a femoral artery. Tracings were made simultaneously on a two-channel writer.

used in 12 experiments. Sometimes it was a tedious process, however, to seat this diaphragm in the preoperative assembly of the pump. This minor defect was remedied by substitution of an 0.038-in. vinyl diaphragm, which can be seated more easily, since a visible change in the translucency of the plastic is noted as the retaining rings are tightened.

In another study,[5] animals occasionally died of coronary artery air embolism due to leaks in the pump, but with experience in assembly and particularly after incorporation of the plastic diaphragm such accidents have been avoided.

SUMMARY

The mechanical features of a diaphragm pump activated by a piston to serve as a mechanical heart have been described together with its use in dogs. In practice this pump has been found to be easy to use and satisfactory to carry the entire output of either the right or left heart. It compares very favorably to other heart pumps.

SUBACUTE AND CHRONIC OSTEOMYELITIS

Treatment with Use of Chemotherapeutic Agents, Antibiotics, and Primary Closure; Follow-Up Report

FRANK D. DICKSON, M.D.
REX L. DIVELEY, M.D.
AND
RICHARD H. KIENE, M.D.
KANSAS CITY, MO.

WE GAVE a preliminary report in 1941 on the treatment of subacute and chronic osteomyelitis by a method in which, after a thorough débridement, sulfathiazole was used systemically and locally and a primary closure of the wound carried out.[1] Twenty-one cases were reported, 18 of which were of hematogenous origin. Primary healing was obtained in 82% of these cases. The following report includes a series of 104 cases, in which the same technique, with primary closure, was carried out in 140 procedures.

In discussing the treatment of subacute and chronic osteomyelitis, a definite distinction must be made between an infection of hematogenous origin and one which complicates a compound fracture or operative intervention. Although the pathological process in the bone may be the same, the reaction of the host is entirely different, for the resistance of the host to the Staphylococcus toxin is much lower in cases of osteomyelitis of hematogenous origin than when the infection follows an open fracture. This report deals entirely with subacute and chronic infections of hematogenous origin.

Before primary closure was advocated, four types of operative treatment were used generally: (1) débridement, followed by repeated packing to provide drainage; (2) the maggot method of Baer; (3) the Dakin-Carrel method, and (4) the Orr method.

The healing time in all these methods was prolonged, thus requiring protracted hospitalization and long periods of invalidism, with resultant great economic loss. The incidence of recurrence was high. It seems that some better method of treatment was desirable. A statement made by Key, Frankel, and Burford[2] suggests that the use of powdered sulfathiazole in a wound is similar to a test-tube experiment in which a concentration of approximately 1,000 mg. of the drug is brought

From the Dickson-Diveley Clinic.

Read before the Section on Orthopedic Surgery at the One Hundred and First Annual Session of the American Medical Association, June 10, 1952.

1. Dickson, F. D.; Diveley, R. L., and Kiene, R. H.: The Use of Sulfathiazole in the Treatment of Subacute and Chronic Osteomyelitis, J. Bone & Joint Surg. **23**:516 (July) 1941.

2. Key, J. A.; Frankel, C. J., and Burford, T. H.: The Local Use of Sulfanilamide in Various Tissues, J. Bone & Joint Surg. **22**:952 (Oct.) 1940.

into contact with any bacteria which may be present in the media. Assuming this statement to be correct, the introduction of sulfathiazole into a properly débrided and saucerized osteomyelitic cavity should inhibit the growth of those bacteria not removed by the mechanical cleaning and make it possible to close the operative wound and secure primary healing.

The original plan was the administration of sulfathiazole by mouth for at least three days before surgery in order to have a therapeutic level in the blood, then a thorough débridement of the local focus and the introduction of powdered sulfathiazole into the wound, followed by primary closure. The sulfathiazole by mouth was continued for two weeks in sufficient doses to maintain a blood level near or above 5 mg. per 100 cc. Since this original procedure was carried out, the only change in treatment has been in the type of chemotherapeutic agent used and in the antibiotic administered. If a predominant organism was cultured, sensitivity tests were carried out and the most suitable agent used in sufficient doses to insure suppression of these organisms, so far as possible.

We have used systemically sulfathiazole, sulfadiazine, penicillin, aureomycin, streptomycin, terramycin, and chloromycetin in the last few years, but the last four antibiotics have not been used in a sufficient number of cases or the patients followed long enough to warrant any conclusions. If no predominant organisms have been cultured, penicillin (400,000 units) is given every four hours on the day preceding surgery and is continued for 12 days after surgery.

The same surgical procedure was followed, and, since this is of basic importance in securing a successful result, it should be reviewed:

1. A tourniquet is applied to the extremity to be operated upon and kept in place until a cast is applied after the operation.

2. The sinus tract or tracts are injected with methylene blue for the purpose of staining and so outlining all necrotic material in the soft parts and in the bone; this minimizes the danger of failing to remove all infected and necrotic material including sequestra.

3. The sinus is completely dissected out down to the infected area in the bone.

4. The involved part of the bone is freely exposed, and, with use of a mallet, chisel, and gouge, all dead and necrotic bone stained by the methylene blue is removed and the cavity saucerized as thoroughly as possible. The rough edges which remain are smoothed off by the use of a slow-moving electric burr.

5. All scar tissue in the soft parts is dissected away as extensively as is necessary to permit healthy tissue to fill in the bone cavity when closure is carried out.

6. The wound is thoroughly irrigated with from 1,000 to 2,000 cc. of normal saline solution to remove all remaining bone chips and mechanically cleanse the wound.

7. About ½ to 1 gm. of sulfathiazole powder is then introduced into the wound, using a nasal insufflator, being sure all areas are covered with a very light coating and that there are no large collections of this powder to act as a foreign body.

8. The deep soft parts are then sutured with interrupted sutures in such a manner as to bring them into as close contact as possible with the denuded area of bone. Frequently, it is necessary to mobilize some normal muscle to fill the cavity. Additional sulfathiazole powder is then insufflated on this layer, and the superficial structures are carefully closed with interrupted sutures. The skin is closed with interrupted cotton suture. A voluminous firm dressing is applied in such a manner as to press the soft parts firmly into the bone cavity.

9. A plaster cast is applied to immobilize the extremity. The tourniquet is removed.

10. The plaster immobilization is maintained for three weeks.

This discussion will be limited to cases in which (1) sulfathiazole by mouth, (2) sulfadiazine by mouth, and (3) penicillin were given before and after operation. In all cases sulfathiazole was used locally.

The study was started in August, 1940, and extends over a 10-year period. The 104 cases of subacute or chronic osteomyelitis were included only when the history left no doubt of the origin being hematogenous in nature. In the few cases in which primary cultures were available, the hemolytic Staphylococcus aureus was the predominant organism. The bacteriological studies taken, however, at the time of the primary closure, revealed that the cultures obtained were so mixed that the determination of a predominant organism was out of the question in all except one case.

The sex distribution was 71 males, or 68.2%, and 33 females, or 31.8%. The bone involvement was multiple in 11 cases. The commonest site of involvement was the femur—58 times, or 42.4%. The next commonest site was the tibia—42 times, or 30.2%—and the third in frequency was the humerus—13 lesions, or 9%.

The age span of patients was from 18 months to 74 years, with the average being 20.9 years. The distribution by decades revealed the following:

Age Span, Yr.	No. of Patients
0-10	23
11-20	34
21-30	26
31-40	14
41-50	5
51-60	1
61-70	0
71-80	1

Of the 140 procedures carried out in cases of subacute and chronic osteomyelitis, in 117 cases, or 83.5%, healing was by primary intention; in 17 cases, or 12%, healing was by secondary intention, and in 6 cases, or 4.3%, the results were considered failures. Of the 117 cases in which healing was by primary intention, the average time from surgery to healing was 18.7 days.

There were 49 procedures in which sulfathiazole was used systemically before and after a thorough débridement and sulfathiazole used locally followed by primary closures. In this series, 37 procedures, or 75.5%, healing was by primary intention, on an average of 19.7 days. There were 8 cases, or 16.3%, in which healing was by secondary intention, with an average healing time of 64.4 days. There were four failures, or 8.2%.

Sulfadiazine was given systemically before and after operation and sulfathiazole used locally in 39 procedures. Primary healing took place in 33 procedures, or 84.6%, with an average healing time of 18.7 days. There were five procedures, or 12.8%, in which healing was by secondary intention. Failure to heal occurred in one case, or 2.6%.

Penicillin was given for one day preoperatively and 12 days postoperatively systemically in 51 procedures, with sulfathiazole used locally. In 47, or 92.1%, healing was by primary intention in an average of 17.9 days. In three cases, or 5.8%, healing was by secondary intention in an average of 44.3 days. Complete failure to heal occurred in one case, or 2%.

Case No.	Age, Yr.	Sex	Duration of Disease	Duration of Present Focus	Location of Focus	Treatment	Result*	Time of Wound Healing, Days	Recurrences
1	25	M	12 yr.	12 yr.	Femur	Sulfadiazine	P	31	None
2	14	M	2 yr.	2 wk. 4 wk.	R. tibia R. tibia	Penicillin Penicillin	P P	30 20	2 yr. later No further recurrences
3	57	M	47 yr.	1 yr.	Femur	Penicillin	P	12	None
4	10	F	7 wk.	7 wk.	Phalanx	Penicillin	P	8	None
5	31	M	25 yr.	6 yr.	Femur Humerus	Penicillin Penicillin	P P	15 17	None None
6	38	F	27 yr.	4 wk.	Femur	Penicillin	P	8	None
7	31	F	27 yr.	27 yr.	Femur	Penicillin	P	22	None
8	9	M	1 yr.	1 yr.	Os calcis	Sulfadiazine	P	10	None
9	17	M	6 mo.	6 mo.	Radius	Sudfadiazine	P	8	None
10	27	M	10 yr.	10 yr.	Femur	Sulfathiazole	P	31	None
11	21	M	5 yr.	5 yr. 1 mo.	L. femur R. femur	Sulfadiazine Sulfadiazine	P P	12 21	None None
12	12	M	3 yr.	2 yr.	Femur	Sulfathiazole	S	70	None
13	12	M	9 yr.	9 yr.	Femur	Sulfathiazole	P	30	None
14	33	M	23 yr.	10 yr.	Tibia	Penicillin	S	46	Skin graft
15	31	M	18 yr.	4 yr.	Tibia	Penicillin	P	35	None
16	30	M	3 wk.	3 wk.	Humerus	Sulfadiazine	P	19	None
17	37	M	29 yr.	4 yr.	Tibia	Sulfathiazole	F	Close in 10 mo.; S. closure with skin flap	None
18	23	M	28 days	6 days	Tibia	Sulfathiazole	P	Healed finally in 10 mo.	Skin graft
19	6	F	2 wk.	2 wk.	Os calcis	Penicillin	P	12	None
20	18	F	12 yr.	12 yr.	Femur	Penicillin	S	39	None
21	17	M	3 yr.	1 yr.	Tibia	Penicillin	P	22	None
22	28	F	23 yr.	10 yr.	Femur	Penicillin	P	13	None
23	47	M	3 yr.	1 yr.	Clavicle	Penicillin	P	9	None
24	11	M	18 mo.	2 wk.	Tibia	Sulfathiazole	P	14	None
25	74	M	55 yr.	55 yr.	Femur	Penicillin	F	S. closure, very slight drainage	
26	36	M	12 yr.	6 mo.	Femur	Sulfadiazine	P	17	None
27	27	F	13 yr.	3 mo.	Tibia	Sulfathiazole	P	40	None
28	14	M	1 yr.	1 yr.	Femur	Sulfathiazole	P	15	Had scar flare-up 1 yr. later, no bone involvement
29	22	M	9 yr.	1 yr.	L. tibia R. tibia	Sulfadiazine Sulfadiazine	S P	65 21	Skin graft None
30	5	F	1 yr.	6 mo.	Femur	Sulfathiazole	P	21	None
31	16	M	3 yr.	1 mo.	Humerus	Penicillin	P	14	None
32	14	M	2 yr.	2 yr.	Femur	Sulfathiazole	P	38	None
33	27	F	14 mo.	14 mo.	Metatarsal	Sulfathiazole	P	15	None
34	13	F	5 yr.	5 yr.	Tibia	Sulfadiazine	P	33	None
35	20	F	8 yr.	8 yr.	Tibia	Sulfathiazole	S	90	None
36	18	M	8 yr.	6 mo.	Tibia	Sulfathiazole	S	71	None
37	41	M	31 yr.	10 yr.	Tibia	Sulfadiazine	S	46	None
38	1	F	6 mo.	6 mo.	Humerus Humerus Humerus	Sulfadiazine Sulfadiazine Sulfadiazine	P P P	27 11 16	6 mo. 18 mo. No further recurrences
39	8	M	2 mo.	2 mo.	Tibia	Sulfathiazole	S	60	None
40	14	M	6 wk.	6 wk.	Femur	Sulfadiazine	P	16	None
41	28	M	14 yr.	2 wk.	Ilium	Sulfadiazine and penicillin	S	75	None
42	3	F	2 wk.	2 wk.	Radius	Penicillin	P	21	None
43	13	M	1 mo.	1 mo.	Femur	Sulfadiazine	P	41	None
44	11	M	2 yr.	2 yr.	Femur	Sulfadiazine	S	45	None
45	28	F	8 yr.	6 mo.	Radius	Sulfadiazine	P	21	None
46	27	F	15 yr.	1 yr. 6 wk.	Humerus Humerus	Penicillin Penicillin	P P	33 14	4 yr. later No further recurrences
47	12	M	1 yr.	1 yr.	Fibula	Sulfathiazole	P	15	None
48	8	F	4 mo.	4 mo. 2 wk.	Tibia Tibia	Sulfathiazole Sulfathiazole	P P	28 23	2 yr. later No further recurrences
49	10	M	1 mo.	1 mo.	Fibula	Sulfadiazine	P	20	None
50	16	M	10 yr.	6 mo.	Tibia	Penicillin	P	35	None
51	36	M	12 yr.	1 yr. 2 wk.	Femur Femur	Penicillin Penicillin	P P	17 21	3 yr. later No further recurrences
52	26	F	2 yr.	6 mo.	Tibia	Sulfathiazole	P	24	Scar, no bone involvement
53	14	M	1 yr.	4 mo.	Femur	Sulfadiazine	P	29	None
54	24	F	11 yr.	3 mo.	Tibia	Sulfathiazole	S	50	None
55	41	M	27 yr.	10 yr.	Femur	Sulfadiazine	P	33	None
56	10	M	1 yr.	1 wk.	Tibia	Penicillin	S	49	None
57	39	F	1 yr.	6 mo.	Rib	Sulfathiazole	P	7	None

Summary of Cases (Continued)

Case No.	Age, Yr.	Sex	Duration of Disease	Duration of Present Focus	Location of Focus	Treatment	Result*	Time of Wound Healing, Days	Recurrences
58	30	M	1 yr.	1 yr.	Femur	Sulfathiazole	P	12	1 yr. later
					Femur	Penicillin	P	19	1 yr. later
					Femur	Penicillin	P	12	2 yr. later
					Femur	Penicillin	P	15	No further recurrences
59	11	M	6 yr.	6 mo.	L. femur	Sulfathiazole	P	14	None
					Humerus	Sulfathiazole	P	14	None
					R. femur	Sulfathiazole	P	13	None
60	13	F	3 yr.	2 mo.	Tibia	Sulfathiazole	P	18	None
61	21	M	14 yr.	14 yr.	Tibia	Sulfadiazine	F	..	Skin slough
					Tibia	Penicillin	P	18	No further recurrences
62	8	F	1 yr.	1 yr.	Radius	Sulfadiazine	P	18	None
63	12	M	1 yr.	6 mo.	Femur	Sulfadiazine	P	20	None
64	7	F	4 yr.	2 yr.	Femur	Sulfadiazine	P	14	None
65	48	F	2 yr.	2 yr.	Femur	Penicillin	P	28	None
66	25	M	1 yr.	6 mo.	Ulna	Sulfadiazine	P	15	None
67	24	M	12 yr.	4 yr.	Humerus	Sulfadiazine	P	27	None
68	40	M	4 yr.	1 yr.	Metatarsal	Sulfathiazole	P	15	None
69	18	F	8 yr.	6 wk.	Femur	Penicillin	P	15	None
70	2	M	1 mo.	1 mo.	Femur	Sulfadiazine	P	25	None
71	12	M	5 yr.	6 mo.	Upper femur	Penicillin	P	14	None
					Lower femur	Penicillin	P	20	None
					Humerus	Penicillin	P	26	None
72	8	F	3 mo.	3 mo.	Tibia	Penicillin	P	21	None
					R. femur	Penicillin	P	15	2 yr. later
				2 wk.	R. femur	Penicillin	P	20	None
73	23	M	11 yr.	2 mo.	Femur	Sulfadiazine	P	30	None
				2 wk.	Ulna	Penicillin	P	10	None
74	5	M	4 yr.	4 yr.	Fibula	Sulfathiazole	P	18	None
					Radius	Sulfadiazine	P	24	None
					Tibia	Sulfadiazine	P	15	None
75	18	M	6 yr.	2 mo.	Femur	Sulfathiazole	P	21	1 yr. later
				2 wk.	Femur	Sulfathiazole	P	21	No further recurrences
76	8	F	6 mo.	6 mo.	Tibia	Sulfadiazine	S	43	2 yr. later
				3 wk.	Tibia	Penicillin	P	18	None
77	21	F	6 yr.	6 mo.	R. femur	Sulfathiazole	P	10	None
				1 yr.	L. femur	Sulfathiazole	P	14	2 yr. later
				2 wk.	L. femur	Sulfadiazine	P	19	None
78	10	M	3 yr.	3 yr.	Tibia	Penicillin	P	15	None
79	24	F	11 yr.	6 mo.	Tibia	Sulfadiazine	S	51	None
80	7	M	3 yr.	3 yr.	Femur	Sulfadiazine	P	14	None
81	31	M	20 yr.	20 yr.	Tibia	Penicillin	P	14	None
82	41	M	27 yr.	6 mo.	Femur	Sulfadiazine	P	13	None
83	40	M	24 yr.	2 mo.	Femur	Penicillin	P	35	None
84	15	M	1 yr.	1 yr.	Tibia	Sulfadiazine	P	19	None
85	9	F	5 yr.	2 mo.	Tibia	Sulfadiazine	P	16	None
86	30	M	23 yr.	2 yr.	Tibia	Sulfadiazine	P	13	None
87	30	F	15 yr.	2 mo.	Tibia	Penicillin	P	13	None
88	5	M	6 mo.	6 mo.	Fibula	Penicillin	P	14	None
89	19	F	1 mo.	1 mo.	Humerus	Penicillin	P	17	None
90	22	M	17 yr.	6 mo.	Tibia	Penicillin	P	21	None
91	6	M	5 yr.	5 yr.	Humerus	Sulfathiazole	P	11	None
				1 mo.	Rib	Penicillin	P	10	None
				1 mo.	Femur	Penicillin	P	11	2 yr. later
				1 mo.	Femur	Penicillin	P	15	No further recurrences
92	14	M	1 yr.	1 yr.	Femur	Sulfathiazole	S	57	1 yr. later
					Tibia	Sulfathiazole	P	14	6 mo. later
					Metatarsal	Sulfathiazole	S	41	1 yr. later
					Tibia	Sulfathiazole	P	41	No further recurrences
					Femur	Penicillin	P	14	Last two operations on same date, no further recurrences
93	5	M	1 mo.	1 mo.	Femur	Sulfathiazole	P	21	None
94	2½	M	5 mo.	4 mo.	Tibia	Sulfathiazole	P	15	None
				5 mo.	Ilium	Sulfathiazole	P	10	None
				5 mo.	Radius and ulna	Sulfathiazole	P	24	None
95	25	M	19 yr.	1 mo.	Femur	Sulfathiazole	P	21	None
96	13	M	6 yr.	10 mo.	Femur	Sulfathiazole	P	22	None
97	13	F	2 yr.	2 yr.	Femur	Sulfathiazole	S	50	None
98	33	M	17 yr.	3 mo.	Humerus	Sulfathiazole	P	21	None
99	32	M	17 yr.	2 wk.	Tibia	Sulfathiazole	P	30	None
100	28	M	7 mo.	7 mo.	Mandible	Sulfathiazole	F	..	.....
101	20	M	8 yr.	1 yr.	Femur	Sulfathiazole	P	15	None
102	16	M	8 yr.	1 yr.	Femur	Sulfathiazole	P	15	None
103	13	M	1 yr.	10 mo.	Femur	Sulfathiazole	F	..	.....
104	13	F	10 yr.	10 mo.	Femur	Sulfathiazole	P	20	None

* Explanation of abbreviations: P, primary; S, secondary, and F, failure.

A critical comparison of the above figures on the three types of treatment used showed the healing time, in days, was approximately the same. However, the percentage of primary healing was 92% when penicillin was used systemically and sulfathiazole locally followed by primary closure. When sulfadiazine was used systemically the percentage of primary healing dropped to 84%. In the cases in which sulfathiazole was used systemically and locally the percentage of primary healing dropped still lower to 75%.

In the 17 procedures in which the healing was by secondary intention, the débridement was adequate but there was a breakdown in skin, requiring secondary closure or healing by granulation. The usual cause of this breakdown was poor circulation due to scar tissue from the repeated infections before the operation. The other cause was skin breakdown from too much tension on the sutures at the time of closure. Failure to heal in the latter group could probably have been prevented by relaxing incisions or primary skin grafts. Of the 17 cases in which healing was by secondary intention, combined sulfadiazine and penicillin was given in one instance, with a healing time of 75 days; in five cases sulfadiazine was administered by mouth, with a healing time of 50 days, and in 8 cases sulfathiazole was given, with a healing time of 44.3 days.

Of the six procedures which were considered failures, two reoperations were done, and it was found that a small sequestrum had been overlooked, and when the sequestrum was removed, healing occurred in both cases by primary intention. Two patients were children, whose conditions were later healed by use of the Dakin-Carrel method of treatment. One patient, aged 74, declined reexploration. He had had a draining sinus for 55 years; after surgery, a large hematoma developed, with a secondary wound breakdown. This was followed by a secondary wound closure, and at the time of discharge, 25 days later, there was only a small amount of drainage—this case was classified as a failure, although the patient's general condition was much improved. The last case was that of a patient who had had osteomyelitis of the tibia for 29 years. He had extensive scar formation, with subsequent breakdown. This finally healed in 10 months but only after the use of an extensive skin flap. He has had no further bone involvement, however.

In 12 cases there was a recurrence of the osteomyelitis in the site that had been operated upon. The relighting of the infection occurred in the 12 cases, from six months to four years after the original operation. All patients were reoperated on, and healing was by primary intention. One of these patients had two recurrences in the original site, and one patient had three recurrences in the same femur. One of the patients, who had multiple sites of osteomyelitis, had a flare-up in each site that had been operated on. One site flared up six months after surgery, and the other two sites flared up one year after the original surgery. Both sites were operated on, and healing was by primary intention.

From our experience we are convinced that the local use of sulfathiazole has been the distinct factor in securing primary healing, but only if a primary closure of the wound is carried out. We doubt very much whether the introduction of sulfathiazole into the wound that is left open or only partially closed does any good, since the sulfathiazole rapidly drains from the wound. The advantage of using sulfathiazole, from our point of view, is that it is absorbed very slowly and its bacterial inhibitory action extends over a number of days. This advantage is naturally lost if the sulfa-

thiazole is removed from the wound by drainage. We also believe that this prolonged bacterial inhibitory action of sulfathiazole is a distinct advantage over the local instillation of penicillin, which is unquestionably rapidly absorbed so that its local effect is maintained for only a short period.

Twelve patients have been under observation, complaining of general malaise and showing redness and induration in the operative scar, indicating, in our opinion, the relighting of the old infection. Nine of the patients had been operated on in our clinic and three elsewhere. It was felt that the work of Weaver and Tyler [3] on experimental osteomyelitis, in which they showed that rabbits with a normal antitoxin titer survived longer than rabbits with a low antitoxin titer when infected with the Staphylococcus organisms, was suggestive. The titer in these 12 cases was determined and found to be under 1.5 international units of Staphylococcus antitoxin. These patients were given Staphylococcus toxoid for the purpose of increasing the Staphylococcus titer. In all these patients the systemic and local reactions disappeared as the titer was elevated and have never gone on to reactivation of the disease. Several of these patients, however, have had recurrences of the local and general symptoms to a mild degree from time to time, but these symptoms have all disappeared with the administration of toxoid. While this is not a sufficiently large series to enable any firm conclusions to be drawn, the results suggest that further study be continued. The administration of this toxoid is started with 0.01 cc. intradermally and the dose increased by doubling every other day until 1 cc. is given subcutaneously. Then 1 cc. is administered at weekly intervals until at least 5 cc. of the toxoid, and usually 10 cc., is given. The amount used depends upon the patient's symptoms and condition. If at any time during the administration of the toxoid a reaction occurs, the next dose is not doubled, but the same dose is used. Two weeks after administration of the Staphylococcus toxoid is completed, the titer is again determined, and if it has not been elevated over the previous level, the course is again repeated.

The majority of the patients included in the report were in the active age and productive period of life. Before the use of primary closure, the period of invalidism was long, as was the time spent in the hospital. Since the cost of hospitalization was increased by the number of dressings required and the amount of supportive therapy administered, the financial loss, not only in actual cost but also in loss of income, was great. With primary closure the majority of the patients were discharged in three weeks and back to productivity within one month. The cost of hospitalization was, therefore, much less and the loss of income kept to a minimum by securing primary healing after operation.

SUMMARY AND CONCLUSIONS

In 104 cases of subacute and chronic osteomyelitis in which 140 débridements and primary closures were carried out, 117, or 83.5%, healed by primary intention.

Injection of the draining sinus with methylene blue followed by a thorough débridement, insufflation of a thin layer of sulfathiazole powder, and careful primary closure is stressed.

3. Weaver, J. B., and Tyler, M. W.: Experimental Staphylococcaemia and Hematogenous Osteomyelitis, J. Bone & Joint Surg. **25**:791 (Oct.) 1943.

When penicillin was used systemically and sulfathiazole locally, the percentage of primary healing was definitely higher than when sulfadiazine or sulfathiazole was used systemically and sulfathiazole locally.

The chemotherapeutic agent or antibiotic used systemically should be adapted to the type of predominant organism depending upon its sensitivity, but if this cannot be determined, the use of penicillin before and after operation is preferred.

The administration of Staphylococcus toxoid in the prevention of recurrences is suggested as a useful adjunct in the treatment of subacute and chronic osteomyelitis, when, after apparent healing, low-grade constitutional symptoms and redness of the scar suggest the probability of the relighting of the disease.

ABSTRACT OF DISCUSSION

DR. T. H. VINKE, Cincinnati: I have been greatly impressed by the excellent results described in this paper. They are superior to those obtained on the orthopedic service at the Cincinnati General Hospital. We have not routinely injected sinus tracts with methylene blue. Perhaps all the necrotic material was not removed as thoroughly as described by the authors, although an attempt was made to do so without the dye. We have not used sulfathiazole powder in the wound for many years, since at times it formed concretions in the tissues and interfered with soft tissue healing.

Any chronic draining sinus always harbors mixed infections. However, the hemolytic Staphylococcus is usually the predominant one. The mixed infections are more difficult to treat than those of only one type of organism.

The determination of the predominant organism is important so that sensitivity tests can be made and the most effective antibiotic used. Far more effective control of the infection can, of course, be obtained by such a procedure.

In the statistical study of 18 of our cases in the past 10 years, I have noticed that in most of our cases the bones of the lower extremities are involved. We have also used antibiotics in very large doses both before and after operation. Primary closure was used in 18 cases in the past 10 years. We have many other cases in which primary closure was not carried out either because of inadequate skin or because of the degree of involvement. The amount of penicillin used varied. At first, of course, when penicillin was scarce, the dose was smaller. The dose varied from 1,000,000 units preoperatively to 15,000,000 units postoperatively. Sulfadiazine was administered in some of the earlier cases, but more recently it has not been used.

At the time of surgery a thorough sequestrectomy and primary closure were done, followed by the application of a plaster cast. In some of these cases more than one surgical procedure was done, at which time an attempt was made to clean out the wound thoroughly. With all due respect to the resident staff, in most cases treatment was carried out by the residents at the Cincinnati General Hospital, and not all of them were supervised by an attending orthopedic surgeon.

In five of these cases, the osteomyelitis developed after a compound comminuted fracture and the situation, as mentioned by the authors, is definitely different from the hematogenous type of infection.

In the cases that I have described the patients were all adults. Of course, the problem of osteomyelitis is entirely different in the adult than in the infant or young child. In young children the infection in bone is likely to respond more closely to infection of the soft tissue than it would later on in life. Consequently, in statistical studies of osteomyelitis, it is always well to differentiate between the condition in adults and in young children.

I thoroughly approve the giving of antibiotics prior to surgery, particularly in view of the fact that infection is likely to spread after surgical intervention and when the wound is closed primarily. Our eventual results are not nearly so good as those described by the authors in that we have had to amputate one lower extremity after an infection following a compound fracture, and in seven cases, slight drainage persisted. However, the average age of our patients is much higher than of those described, which might also make some difference. Some of the cases

reported are of children under 5 years of age, but even taking this into consideration, the reported results are far superior, and I commend the authors for their excellent results.

In some of our cases, we have used full-thickness skin grafts when the skin was thin, hard, and scarred, and when primary closure was not possible.

We have not used Staphylococcus toxoid for the purpose of increasing the Staphylococcus titer. From the information I have obtained, the osteomyelitis itself produces far more toxoid than could be administered. The small amount given could not materially affect the progress of the disease. If this theoretical statement is correct, then the good results presented by the authors are due to the effects of thorough surgical débridement and to the antibiotics introduced both preoperatively and postoperatively.

The primary closure, of course, to many of us seemed a rather hazardous thing to do, but with experience of thoroughly controlling the infection by surgery and antibiotics, primary closure can be done and is desirable in cases of subacute and chronic osteomyelitis.

DR. EARL S. LEIMBACHER, Joliet, Ill.: The possibilities of adequate surgery, when augmented and fortified by chemotherapy, in its broadest sense, including the use of antibiotics, open up a field of almost unlimited possibilities in cases which were long drawn out in the past.

From our experience in the last few years, I think we can draw four main concepts. There are others, of course, that will be drawn in the future.

First, I agree wholeheartedly that adequate surgery, with the injection of methylene blue and complete resection of all scar tissue, necrotic tissue, and the like, must be done.

Secondly, I take issue with one word in the paper. That is the use of the term "suppressant" doses of penicillin. I would say that we should use "devastating" doses, and I think the authors have certainly done that when you stop to consider that they used 400,000 units of penicilin six times a day, or a total of 2,400,000 units a day.

One word of warning here: If any of the antibiotics or therapeutic agents are to be given, they must be used not in suppressive doses but in devastating doses, both locally and internally, otherwise a penicillin-resistant strain of bacteria may develop.

The third point of importance is the obliteration of dead space, and this should be done by means of live muscle and must be done without tension. I have always used a relaxing incision, with a primary split-thickness skin graft on the side, in those cases in which the skin and soft-tissue edges did not fall together almost of their own accord. In all cases I have used absorbable surgical (gut) sutures.

The fourth main concept we must take into account is that of our increase in knowledge in the use of blood transfusion and our idea of preoperative and postoperative care. I think the failures reported in his series can be traced back to something that has gone amiss in one of the above four points.

DR. REX L. DIVELEY, Kansas City, Mo.: The hour is late, and I don't think there are very many questions that should be brought out, but I think that this method of treatment was brought to our attention when sulfonamides were first brought to the attention of the average surgeon. It seemed to me that when the abdominal surgeon felt he didn't have a good, adequate result in the operating room, he always told the resident or his assistant to give the patient sulfonamides over a certain period of time. The same is true at present for penicillin.

Frankly, if we do proper, adequate débridement, I don't think we will need penicillin. I don't think we will need the sulfonamides, except for the systemic effect that they might get.

One of these discussers has very adequately expressed the thought that blood transfusion is an excellent thing. It probably does just as much good at the operating table in prophylactic relief of the system as the antibiotic factors.

I think that the use of penicillin, sulfathiazine, or any of the sulfonamide drugs actually just covers up for the surgeon who doesn't do an adequate job at the surgical table.

SURGICAL MANAGEMENT OF SHOULDER GIRDLE SYNDROMES

New Operative Procedure for Hyperabduction, Costoclavicular, Cervical Rib, and Scalenus Anticus Syndromes

JERE W. LORD Jr., M.D.
NEW YORK

BEYER and Wright [1] in 1951 discussed the neurovascular syndromes of the shoulder girdle from the anatomical and clinical viewpoints and outlined the medical management of them. It was their belief that an accurate differential diagnosis could be made on the basis of a careful history and physical examination and that a favorable response to conservative measures could be expected in the majority of cases.

Although the diagnosis of the cervical rib syndrome was made by Willshire [2] in 1860 and by Gruber [3] in 1869, it was not until 1905 that Murphy [4] described changes in the neurovascular mechanism occurring as a result of pressure between a cervical rib and the scalenus anticus muscle. Naffziger and Grant [5] and Ochsner, Gage, and DeBakey [6] in 1935, pointed out the fact that the scalenus anticus muscle without a cervical rib could be responsible for pressure on the neurovascular bundle, with consequent clinical symptoms. Falconer and Weddell [7] in 1943 demonstrated for the first time that postural changes without an anatomic defect could precipitate neurovascular symptoms in the upper extremity as a result of narrowing of the space between the clavicle and first rib by a backward and downward thrust of the shoulders. They coined the term costoclavicular syndrome for this

From the Department of Surgery, New York University Post-Graduate Medical School, and the Fourth Division of Bellevue and University Hospitals.

Read before the Section on Surgery, General and Abdominal, at the One Hundred and First Annual Session of the American Medical Association, Chicago, June 11, 1952.

1. Beyer, J. A., and Wright, I. S.: Hyperabduction Syndrome, with Special Reference to Its Relationship to Raynaud's Syndrome, Circulation **4**:161, 1951.

2. Willshire: Supernumerary First Rib, Clinical Records, Lancet **2**:633, 1860.

3. Gruber, W.: Über die Halsrippen des Menschen mit vergleichend anatomischen Bemerkungen, Mém. Acad. imp. d. sc. St. Petersburg, 1869, Vol. 12.

4. Murphy, J. B.: Case of Cervical Rib with Symptoms Resembling Subclavian Aneurysm, Ann. Surg. **41**:399, 1905.

5. Naffziger, H. C., and Grant, W. T.: Neuritis of the Brachial Plexus Mechanical in Origin: The Scalenus Syndrome, Surg., Gynec. & Obst. **67**:722, 1938.

6. Ochsner, A.; Gage, M., and DeBakey, M.: Scalenus Anticus (Naffziger) Syndrome, Am. J. Surg. **28**:669, 1935.

7. Falconer, M. A., and Weddell, G.: Costoclavicular Compression of the Subclavian Artery and Vein: Relation to the Scalenus Anticus Syndrome, Lancet **2**:539, 1943.

group of cases. In 1945 Wright [8] described the hyperabduction syndrome produced by holding the arms in the position of hyperabduction with the elbows flexed or with the plane of their long axes parallel to the body. He observed ischemic changes in the fingers of some patients who slept for long hours in this position, as well as of others whose occupation demanded the use of their arms in the position of hyperabduction, namely, telephone operators, grease-pit mechanics, riveters, ballet dancers, etc.

Regardless of which shoulder girdle syndrome is incriminated, and in some patients there may be two or more at fault, symptoms may be due to intermittent arterial occlusion, which occasionally becomes persistent due to thrombosis of the subclavian or axillary artery; to intermittent venous occlusion, which likewise may sometimes become persistent due to thrombosis, and to neurologic symptoms due to pressure on the brachial plexus, usually noted in the areas supplied by the eighth cervical and first thoracic nerves. Fatigue and weakness of the hand may be prominent in the patient's complaints; in other patients, numbness, paresthesias, and atrophy of the intrinsic muscles of the hand may predominate. When arterial insufficiency is marked, ischemic changes progressing to frank gangrene have occasionally been observed. Venous occlusion, temporary or permanent, usually is evidenced by edema, fatigue, and cyanosis. Rarely, aneurysmal formation of the subclavian artery develops beyond the point of partial obstruction due to pressure exerted by the scalenus anticus muscle and a cervical rib. Inquiry into the type of work and sleeping habits will point, in some cases, to an aggravation noted during the assumption of the position of hyperabduction or the costoclavicular position.

Differential diagnosis has been clearly stated by Beyer and Wright [1] and includes a careful analysis of the arterial circulation to the hand while performing the maneuvers designed to reveal pressure exerted by the scalenus anticus muscle, in the costoclavicular space and in the position of hyperabduction. A roentgenological examination to demonstrate the presence of a cervical rib is routinely performed. Venous obstruction is sometimes evident on examination as a result of the development of superficially located collateral veins around the shoulder area and by the measurement of venous pressure. Neurological abnormalities are readily detected by examination of the motor and sensory function of the hand. Cervical disc and arthritic changes in the cervical vertebrae may simulate the neurological changes observed in the shoulder girdle syndromes.

Haggart,[9] Beyer and Wright,[1] and others have stressed the favorable results to be obtained in the majority of patients by conservative measures. Improvement in posture, change in sleeping or working habits, and muscle reeducation will help many patients. Surgical therapy should be reserved for the minority of patients who fail to obtain symptomatic relief from medical therapy and for the occasional patient in whom a frank arterial or venous occlusion develops.

8. Wright, I. S.: The Neurovascular Syndrome Produced by Hyperabduction of the Arms: Immediate Changes Produced in 150 Normal Controls, and Effects on Some Persons of Prolonged Hyperabduction of the Arms as in Sleeping, and in Certain Occupations, Am. Heart J. **29**:1, 1945.

9. Haggart, G. E.: Value of Conservative Management in Cervicobrachial Pain, J. A. M. A. **137**:508, 1948.

Historically, operative techniques included resection of the cervical rib, later in conjunction with sectioning the scalenus anticus muscle. In the period from 1935 to 1940, the use of simple division of the scalenus anticus muscle was carried out in many areas in this country, and, although some patients experienced relief, many failures were noted, possibly in some instances due to the fact that the symptoms were caused by another shoulder girdle syndrome other than the scalenus anticus syndrome. Telford,[10] who is one of the most thorough students of the shoulder girdle syndrome, states:

> The importance of the scalenus anterior syndrome has been over-emphasized. If operative treatment is limited in all cases to anterior scalenotomy the results will be disappointing. If operation is advised it should be performed without rigid and preconceived ideas, through an adequate incision, and with exploration wide enough to allow thorough investigation of the cause of pressure.

If one analyzes the anatomical structures through which the subclavian and axillary artery and vein must pass, then it is evident that no single operative procedure can be successful in all cases of the shoulder girdle syndromes. Firstly, the subclavian artery passes behind the scalenus anticus muscle and over the first rib, a space which may be considerably narrowed by the presence of a cervical rib or of a fibrous extension of a short cervical rib; secondly, it must pass between the first rib posteriorly and the clavicle and subclavius muscle anteriorly; thirdly, it passes beneath the pectoralis minor muscle near its insertion into the coracoid process. The subclavian vein has many of the same anatomical landmarks, except that it must pass anteriorly to the scalenus anticus muscle and therefore lies in a snug compartment between it and the subclavius muscle.

It occurred to Wright, Huebner, and Lord[11] that a satisfactory "space making" procedure for the subclavian artery and vein and the brachial plexus could be developed by total resection of the clavicle, division of the scalenus anticus muscle, and mobilization of the subclavian artery downward. Complete removal of the periosteum was found desirable to prevent regeneration of the clavicle. This procedure eliminated angulation behind and pressure on the artery by the scalenus anticus muscle, with rolling downward and forward of the vessel. The presence of a cervical rib could then have no ill effects. Pressure on the subclavian artery and vein by the first rib and clavicle was relieved by resection of the clavicle, which permitted anterior displacement of the vessels and of the subclavius muscle. Finally, not only by elimination of the above two anatomically fixed points is the artery lengthened into the axilla, but it is also lengthened after claviculectomy by the inward and forward movement of the shoulder girdle toward the chest wall, which further relaxes the pectoralis minor muscle. As a result of the changes produced by the operation described in this paper, only one radial artery can be obliterated postoperatively by maneuvers which preoperatively obliterated the radial pulse in 13 extremities of nine patients.

The operation is carried out by an incision over the length of the clavicle, with subperiosteal resection of the bone (Figs. 1, 2, and 3). Then the periosteum is

10. Telford, E. D., and Mottershead, S.: Pressure at the Cervicobrachial Junction: Operative and Anatomical Study, J. Bone & Joint Surg. **30B**:249, 1948.

11. Lord, J. W., Jr.; Heubner, R. D., and Wright, I. S.: New Surgical Concept in the Management of Refractory Cases of the Shoulder Girdle Syndromes, to be published.

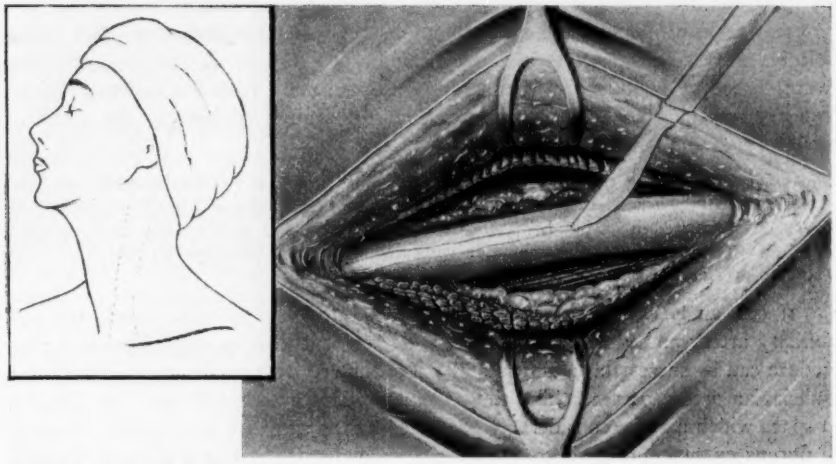


Fig. 1.—Incision of periosteum to expose the clavicle. Insert shows the skin incision over the clavicle. (The Macmillan Company gave permission for reproduction of the photographs, which were published in the "New York Academy of Medicine, Diseases of the Circulatory System," 1952.)

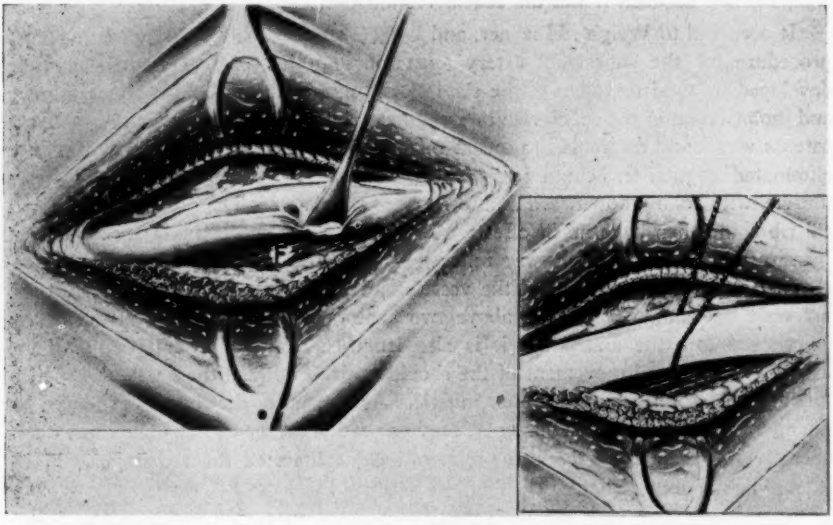


Fig. 2.—Reflecting periosteum from clavicle; subclavius muscle (*F*). Insert shows section of clavicle with gigli saw.

completely and carefully removed to avoid injury to the subclavian vein (Fig. 4). The scalenus anticus muscle is sectioned (Fig. 5) and the subclavian artery mobilized downward (Fig. 6). Postoperative x-rays have shown no evidence of bony regeneration during the first six postoperative months (Fig. 7). Function of the

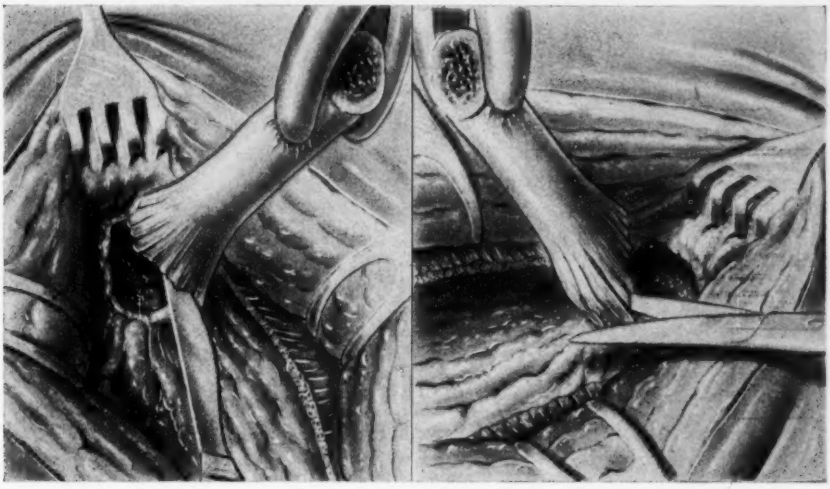


Fig. 3.—Left, removal of medial segment of clavicle. Right, removal of lateral segment of clavicle.

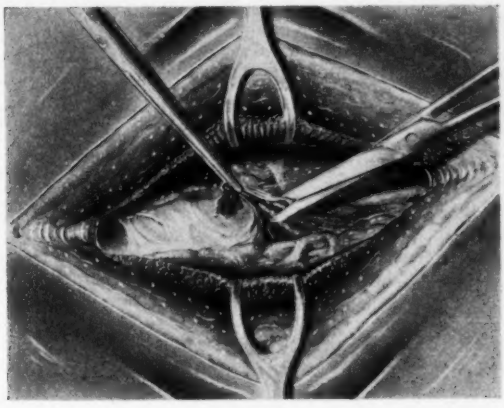


Fig. 4.—Excision of periosteum from clavicular bed.

arms and shoulders has been excellent and, except for temporary aching discomfort in the shoulder areas in two heavily muscled men, no disability has been noted. No disfigurement has resulted from the procedure (Fig. 8).

During the early period of development of this operative procedure, an incomplete operation was carried out, namely, partial resection of the middle half of the

clavicle without removal of the periosteum, and later it was necessary in two patients to reoperate and remove the remaining segments of the clavicle and the periosteum, with complete relief of the arterial obstruction.

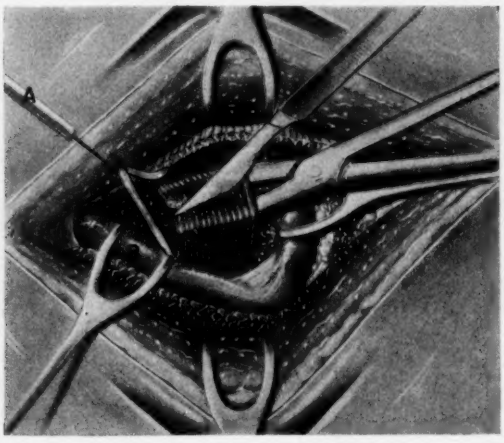


Fig. 5.—Scalenus anterior muscle sectioned. Phrenic nerve (*A*), subclavian vein (*B*), external jugular vein retracted (*C*).

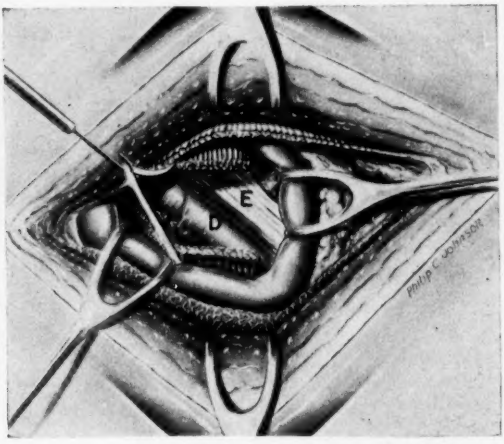


Fig. 6.—Exposure of subclavian artery (*D*) and brachial plexus (*E*).

Resection of the clavicle alone for exposure of vascular lesions of the subclavian artery has been practiced by Elkin [12] and Shumacker,[13] without functional

12. Elkin, D. C., and Cooper, F. W.: Resection of the Clavicle in Vascular Surgery, J. Bone & Joint Surg. **28**:117, 1946.

13. Shumacker, H. B., Jr.: Resection of the Clavicle: With Particular Reference to the Use of Bone Chips in the Periosteal Bed, Surg., Gynec. & Obst. **84**:245, 1947.

derangement of the shoulder girdle, and Gurd [14] emphasized that the clavicle was one of the readily spared bones of the skeletal system. Pipkin [15] in 1951 reported a successful result following claviculectomy wherein arterial and venous obstruction had been due to nonunion of a fractured clavicle. Campbell [16] in 1949 performed a partial claviculectomy for nonunion which had resulted in neurological

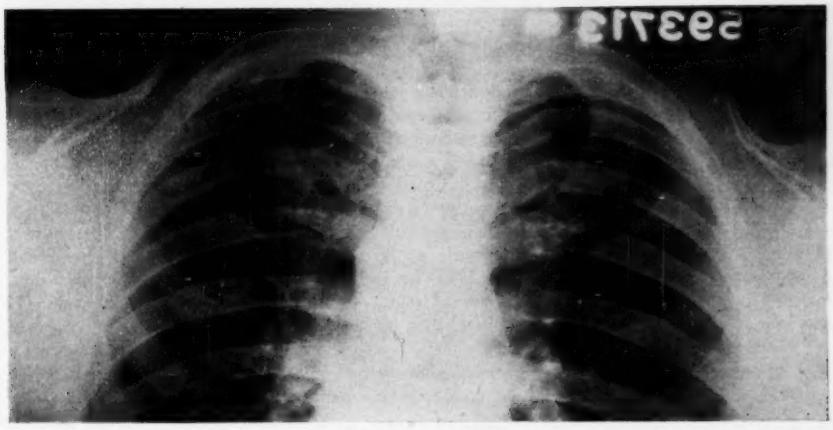


Fig. 7.—Roentgenogram taken six months postoperatively, showing no evidence of regeneration of either clavicle.

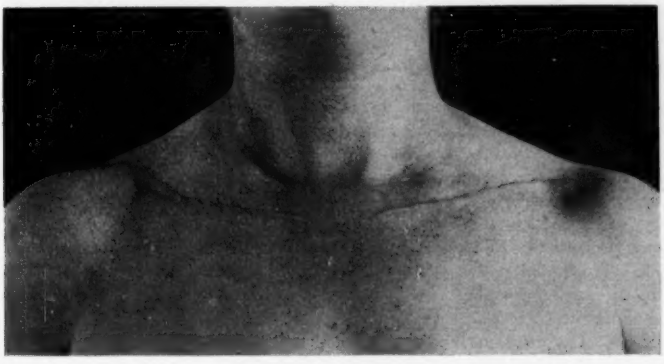


Fig. 8.—There is no evident disfigurement from total claviculectomy.

symptoms and signs in the arm and hand related to pressure on the brachial plexus by bony callus and displacement of the inner ends of the two fragments of the

14. Gurd, F. B.: Surplus Parts of the Skeleton: A Recommendation for the Excision of Certain Portions as a Means of Shortening the Period of Disability Following Trauma, Am. J. Surg. **74**:705, 1947.

15. Pipkin, G.: Tardy Shoulder-Hand Syndrome Following Ununited Fracture of the Clavicle, J. Missouri M. A. **48**:643, 1951.

16. Campbell, E.; Howard, W. P., and Birklund, C. W.: Delayed Brachial Plexus Palsy Due to Ununited Fracture of the Clavicle, J. A. M. A. **139**:91, 1949.

clavicle. A satisfactory result followed the operation. McCleery and his associates [17] described a procedure for lessening pressure on the subclavian vein by excision of the subclavius muscle and anterior scalenotomy with favorable results.

REPORT OF CASES

Three illustrative cases follow.

J. R., a 33-year-old white man, employed as a polisher on an automobile assembly line, was first seen in March, 1950. His job required that he hold a 35-lb. (15.9 kg.) buffing machine at arms length at an angle of 130 degrees to his body against the body of an automobile. In March, 1948, he reported to the plant physician, complaining of intermittent aching and numbness of both hands. A diagnosis of neuritis was made. During a short absence from work in November, his symptoms subsided. Upon returning to work, there was a recurrence of symptoms, with a gradual increase of easy fatigability and aching pains involving the hands, shoulders, and arms. He also noticed blanching of the hands while working. This was followed by rubor when he rested. He denied any color change with exposure to cold. The symptoms usually subsided after a week-end rest. He was in the habit of sleeping with his arms in the position of flexed hyperabduction, and he frequently awakened during the night with a feeling of numbness in his hands. In October, 1949, he had a complete neurological examination, including x-rays of the shoulders and cervical spine. A diagnosis of neuralgia was made. It was then suggested that he change the nature of his work.

TABLE 1.—*Oscillometric Readings*

	A. Preoperative (3/6/50)		B. Postoperative (4/20/51)	
Wrist at	Rt.	Lt.	Rt.	Lt.
0°	1.8	2.0	4.5	4.5
90°	0.2	0.0	4.5	4.5
135°	0.0	0.0	4.5	4.0
180°	0.0	0.0	3.5	3.5

Physical Examination.—The patient was a heavy-set, muscular white man. The general examination was entirely unremarkable, and the positive findings were limited to the upper extremities. Inspection of the shoulder girdles revealed that the lateral portions of both clavicles seemed to be curved more posteriorly than normal. Both the hands and the arms were of normal color and temperature, and there were no trophic skin changes. The radial and ulnar arteries were patent by the Allen test. The radial pulses were easily blocked when the arms were abducted to a position of 90 degrees or more, when extended either anteriorly or laterally to the trunk. The radial pulses were also blocked when the patient was tested for hyperabduction in the supine position. Oscillometric readings confirming the obliteration of the pulses are recorded in Table 1A.

Although the exact mechanism of the symptomatology was not clear, it suggested a structural abnormality of the shoulder girdles, which caused pinching or pressure on the neurovascular structures when the arms were held in a position of hyperabduction. The nature of his work caused a hypertrophy of the muscles of the shoulder girdle, and possibly there was some encroachment upon the neurovascular structures. He was advised to discontinue heavy manual work.

Course.—When the patient was seen again in January, 1951, for reevaluation, he was employed as an oil sander. The job required holding his hands in all positions, but it did not involve lifting heavy objects. His symptoms, while considerably diminished, were still present. He also described a feeling of stiffness in the shoulders and neck, with occasional swelling of

17. McCleery, R. S.; Kesterson, J. E.; Kirtley, J. A., and Love, R. B.: Subclavius and Anterior Muscle Compression as a Cause of Intermittent Obstruction of the Subclavian Vein, Ann. Surg. **133**:588, 1951.

the hands associated with numbness and tingling. Reexamination revealed no new findings. Since the symptomatology had not diminished to any significant degree, exploration of the shoulder girdle seemed advisable. At operation on March 1, it was observed that the left subclavian artery was undergoing repetitive compression between the clavicle and the first rib. Accordingly, a partial excision of the left clavicle was performed, with division and partial removal of the left scalenus anticus muscle and mobilization of the left subclavian artery. Eight days later, on March 9, a similar operation was performed on the right side. The postoperative course was uneventful. Immediately after each operation the hand became symptom free on side of operation. Within a few days it was possible to elevate the patient's arms to a position of 90 degrees without blocking the radial pulses, and one week after the operation there was no obliteration of the radial pulses upon elevation of the arms to 180 degrees. The postoperative oscillometric readings showed remarkable improvement and confirmed the presence of a strong radial pulse in all positions (Table 1B).

Follow-up during the next few months revealed excellent radial pulses in all positions of hyperabduction. The previous symptoms in the hands were absent, but the patient complained of pinching in the shoulder girdles upon leaning forward to tie his shoelaces or when lifting heavy objects. By June, there was evidence of a bony regrowth of the remaining portions of the clavicles. The patient was therefore readmitted to the New York Hospital in July, and the remaining portions of the clavicles and the periosteum were removed. The patient improved remarkably, except for mild discomfort of the shoulders and easy fatigability. The pulses at the wrist were greater that at any time previously. Oscillometric readings in October, 1951, were 5.0 in all positions bilaterally.

Comment.—This patient suffered from a hyperabduction syndrome, which was treated conservatively for a one-year period without significant improvement. The severity of the symptoms and the patient's inability to obtain relief from change of work warranted an exploratory operation of the shoulder girdles. The second operation was indicated when it became clear that the clavicular stumps were pinching the intervening tissue, causing discomfort. Since removal of the clavicles, it has been impossible to dampen the pulses at the wrist.

M. R., a 44-year-old white nurse, was first seen on March 21, 1951, with a chief complaint of numbness and tingling of the second and third fingers of the right hand of six months' duration. Subsequently, blanching of the affected fingers occurred on exposure to cold. Three months previously, while bowling, she experienced right shoulder and arm pains, after which typing and grasping small objects became increasingly difficult. One month previously, all fingers of her right hand became involved. The numbness and tingling increased, and a feeling of stiffness in the fingers and a "constricted" feeling in the arm developed. She was unable to type more than a sentence at a time. Two weeks previously, the pains become worse, and the right hand became cold.

Examination.—Physical examination revealed a well-developed, well-nourished, white woman, who appeared depressed and discouraged. The blood pressure in the right arm was 116/80 and in the left arm 126/86. The pertinent findings on examination were limited to the upper extremities. There was fullness in the right supraclavicular region with prominence of the superficial veins over the right shoulder girdle. The right midbrachium measured 2 cm. larger than the left. The radial and ulnar pulses on the right were faintly detectable. The right hand was cooler than the left and was slightly cyanotic. On hyperabduction the right hand became pale, while the left hand remained pink. When it was dependent, the color returned slowly. The right radial pulse disappeared on even slight abduction of the arm. The left radial artery could be blocked transiently at 180 degrees hyperabduction. Testing for the costoclavicular syndrome revealed blocking of the left radial artery. X-rays of the neck revealed a large cervical rib on the right, articulating with a bony process projecting upward and backward from the posterior aspect of the first rib (Fig. 9). On the left there was a smaller cervical rib articulating with the posterior portion of the first rib.

Oscillometric readings of the upper extremities in the various positions of hyperabduction are shown in Table 2A.

The diagnosis of bilateral cervical ribs was evident. There was some indication that the hyperabduction mechanism was contributing to her disability. The costoclavicular test was positive on the left and may have been positive on the right, but because of the nearly absent pulse on the right, the test could not be evaluated. Because of the evidence of vascular occlusion, probably involving the subclavian artery and vein, arrangements were made to admit the patient to the hospital for an exploratory operation.

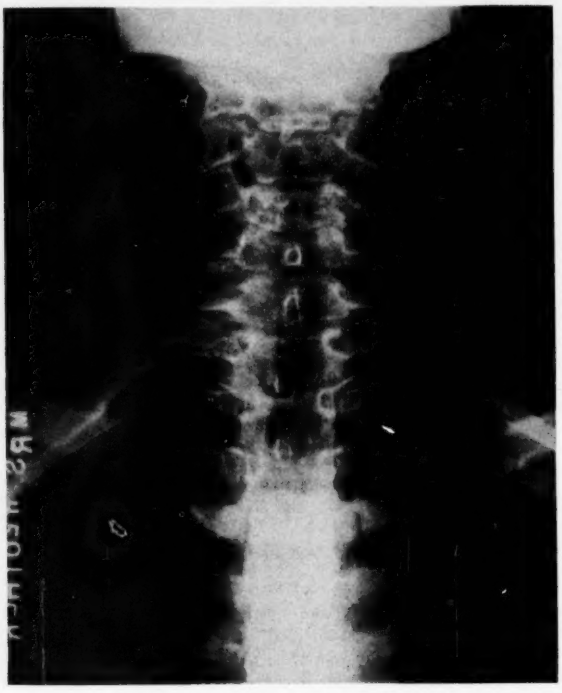


Fig. 9.—Roentgenogram showing a large cervical rib on the right and a small one on the left.

TABLE 2.—*Oscillometric Readings*

	Preoperative				Postoperative			
	A (3/21/51)		B (4/27/51)		C (5/14/51)	D (9/26/51)	E (2/29/52)	
Wrist at	Rt.	Lt.	Rt.	Lt.	Rt.	Rt.	Rt.	Lt.
0°	0.1	3.0	0.7	2.8	1.5	1.2	2.0	3.0
90°	0.0	3.0	0.7	2.8	1.5	1.0	2.0	3.0
135°	0.0	2.5	0.7	2.5	1.5	0.5	1.5	3.0
180°	0.0	2.0	0.7	2.5	1.5	0.5	1.5	2.0

Course.—Ten days later, while awaiting admission to the hospital, she was admitted as an emergency when her right hand suddenly became painful, cold, cyanotic, and useless. She was unable to hold a pen in her hand to sign her name. Examination revealed complete absence of pulses in the right arm, and the blood pressure was no longer obtainable. Oscillometric readings in the right wrist were zero in all positions. She could not open or close her fist. It was our impression that complete thrombosis of the subclavian and axillary artery had occurred. Immediate exploration seemed indicated. Accordingly, on March 31, a resection of the middle

third of the right clavicle, with division of the right scalenus anticus and division of a fibrous band extending from the cervical rib to the first rib, was performed. The right subclavian artery was mobilized. The significant findings at operation were as follows: A broad, thin fibrous band extended from the cervical rib to the first rib and flattened and pinched the subclavian artery between it and the cervical rib. Distal to this point of compression there was a pulsating fusiform aneurysmal dilatation of the subclavian artery. In addition, it was also noted that the space between the clavicle and the first rib was so tight that it was impossible to insert the tip of the index finger between the two bones. For this reason it was deemed advisable to resect the clavicle and to divide the fibrous band so that adequate space would be available for the subclavian artery and vein, as well as the adjacent portions of the brachial plexus. Resection of the cervical rib did not seem to be indicated, since it no longer exerted pressure on the neurovascular structures.

The immediate postoperative course revealed only a slight favorable change in the patient's signs and symptoms. The oscillometric readings remained the same. The hand continued to be pale, slightly cyanotic, cold, and useless. It was felt that a thrombosis must have extended distal from the aneurysm and involved the axillary artery. On the third postoperative day, the right shoulder and upper arm became swollen and the superficial veins more prominent. Several of these veins were definitely thrombosed. Anticoagulant therapy was begun with ethyl biscoumacetate (tromexan® ethyl acetate). Gradual improvement occurred, and she was discharged on April 12. Anticoagulant therapy was continued for one month on an ambulatory basis. The hand and shoulder pain disappeared, although the right hand remained pale and cold compared with the left hand. At the time of discharge she could do little more than sign her name. Oscillometric readings taken one month postoperatively are recorded in Table 2*B*. At this time the right radial pulse was again present. She felt much better and was able to type one-half page without discomfort. The hand still became pale and cold on exposure to cold.

By May 14, the readings at the right wrist were 1.5 in all positions (Table 2C). By June 15, she returned to work and was without limitation, doing all her own housework and secretarial work. However, at this time it was noted that a bony mass was developing in the supraclavicular region at the point where the right clavicle had been partially resected. This appeared to be callus formation at the site of the remaining periosteum. Oscillometric readings at this time again showed a significant decrease, although the radial pulse was still present in all positions but much weaker than that on the left side. Despite this, she did well until Sept. 1, when she noted a gradual recurrence of the same symptoms of the shoulder and arm pain with cramps, easy fatigability, and coldness in the hand. Examination on Sept. 26, revealed the previously noted bony mass to be considerably larger and painful on palpation. There was also increased prominence of the superficial veins over the right shoulder girdle. Oscillometric readings were found to be decreased, with definite evidence of blocking of the radial pulse at 135 to 180 degrees hyperabduction (Table 2D). It seemed likely that the recurrence of symptoms was due to pressure on the neurovascular structures, caused by regeneration of the clavicle. On the basis of the previous experience with Case 1, it was therefore decided to reoperate and totally excise the right clavicle and the periosteum. This was done on Oct. 17, without difficulty. She was discharged on the seventh postoperative day with complete relief of her preoperative symptoms. Since then, she has made excellent progress. She is able to carry on all of her regular office work and has added heavier household duties, which have included scrubbing the kitchen floor with her right arm, without untoward symptoms. Although the veins are still prominent over the right shoulder girdle, the radial pulse is excellent and is nearly as strong as the left radial pulse. It cannot be obliterated by moving the arm in any position. Oscillometric readings on Feb. 29, 1952, are recorded in Table 2E. The only significant residual complaint has been persistence of the Raynaud's phenomenon on exposure to cold. This involves the right first and second fingers and has not responded to the above described surgical procedure.

Comment.—This patient was operated upon on an emergency basis because of acute arterial thrombosis of the right axillary artery. This episode was a complication of the cervical rib syndrome occurring in association with the hyperabduction syndrome. The bony regeneration of the right clavicle resulted in a recurrence of

symptoms after a four-month interval due to renewed pressure on the neurovascular structures. Excision of the entire clavicle by a second operation, as in Case 1, gave prompt relief and again demonstrated the impossibility of dampening the pulses in the upper extremity in any position after removal of the clavicle.

P. K., a 20-year-old white woman student was first seen by us on July 3, 1951. Six months previously, in January, suddenly a painless swelling of the left arm had developed. This was associated with an upper respiratory infection and temperature of 102 F. Within two weeks the left arm became cyanotic, with associated prominence of superficial veins. She gave a history of sleeping with her arms in a position of hyperabduction. She also spent several hours each day swimming and practicing ballet or acrobatics. She noticed that her arms "felt heavy" when hyperabducted for short periods.

In March, she was given anticoagulant therapy because of the persistent swelling of the left arm. At this time, the hyperabduction syndrome was discovered. The right radial pulse blocked out at 135 degrees and the left radial at 90 degrees, although both radials were strong in adduction. Oscillometric readings confirmed the presence of a bilateral hyperabduction syndrome (Table 3A).

On June 17 she was hospitalized, and a venogram and an arteriogram were performed with the patient under anesthesia. It was noted that with the patient under anesthesia the radial pulse could not be obliterated. (This is a common finding, probably due to relaxation or readjustment of the structures of the shoulder girdle while under anesthesia.) The arteriogram performed by forceful retrograde injection of iodopyracet (diodrast®) into the brachial artery revealed no arterial compression in the shoulder girdle in adduction or hyperabduction. The venogram revealed obstruction of the first portion of the subclavian vein at the junction of the clavicle and the first rib (Fig. 10).

TABLE 3.—*Oscillometric Readings*

	Preoperative				Postoperative	
	A (8/17/51)		B (7/3/51)		C (9/13/51)	
Wrist at	Rt.	Lt.	Rt.	Lt.	Rt.	Lt.
0°	3.5	2.5	3.5	0.5	3.5	0.5
90°	3.0	0.8	3.0	0.3	3.0	0.5
135°	2.5	0.0	2.5	0.0	2.0	0.2
180°	0.0	0.0	0.0	0.0	0.0	0.1

The day after the arteriogram was taken, the left radial and ulnar arteries were faint and the oscillometric readings at the left wrist taken in adduction diminished from 2.5 to 0.5. It was believed that the brachial artery had been damaged due to the trauma of the arteriogram. The left hand became cool, compared with the right.

She was treated conservatively for the next few weeks and when seen by us on July 3, the following findings were noted: The left arm and shoulder were slightly swollen. The left midbrachium measured 2 cm. larger than the right in circumference. The superficial veins were prominent over the left shoulder and arm. On dependency, the left arm showed a mild rubor, and on elevation there was considerable pallor. The left radial pulse was present, but faint, while the pulsation in the ulnar artery was absent. The Allen test revealed very sluggish filling of the left hand by the radial and ulnar arteries. The left hand was cooler than the right. Hyperabduction confirmed the previous findings except that the left radial pulse was now obliterated at 45 degrees on palpation, although the oscillometer showed a reading of 0.3 at 90 degrees of abduction (Table 3B).

The patient had a hyperabduction syndrome bilaterally, with marked changes on the left complicated by a subclavian or axillary vein thrombosis. In addition, there was further impairment of the arterial supply to the left hand secondary to the trauma of the arteriogram.

Course.—On July 23, the patient underwent exploration, and resection of the entire left clavicle and the periosteum, in addition to anterior scalenotomy and mobilization of the left

subclavian artery, was performed. The patient made an uneventful recovery and has shown considerable improvement since then.

Oscillometric readings on Sept. 13 (Table 3C) revealed for the first time that complete blockage failed to occur on hyperabduction of the left arm. In addition, the left brachial and ulnar pulses were easily detected in all positions of hyperabduction. The right radial pulse continued to block out at 135 degrees hyperabduction. At present the patient is pleased with the result and prefers the left arm to the right. She is now able to hyperabduct the left arm without discomfort, although she has been warned to be careful about maintaining the right arm in a position of hyperabduction. She has requested that the procedure be repeated on the right side, but we have felt that indications to perform a similar procedure on the right are not sufficiently urgent to justify this.

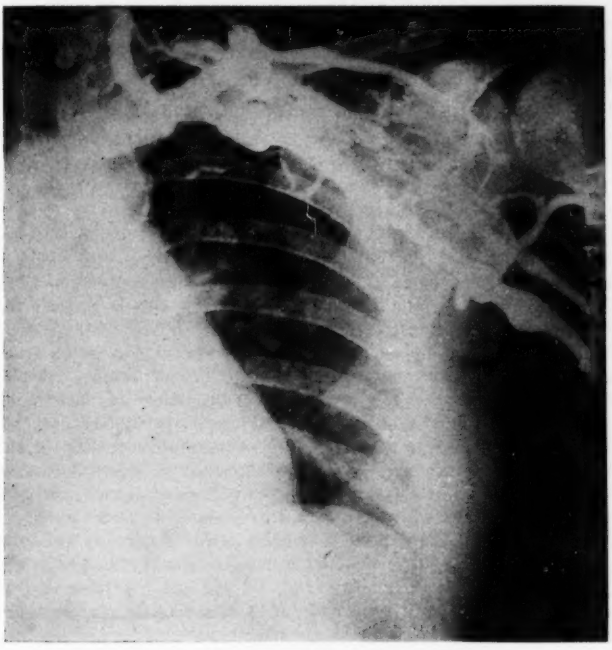


Fig. 10.—Venogram showing obstruction of the subclavian vein at the junction of the clavicle and the first rib.

Comment.—This case demonstrates both arterial and venous compression in the shoulder girdle. Although the arterial compression was intermittent, nevertheless, sufficient damage occurred to the subclavian vein at the point where the clavicle crosses the first rib that venous thrombosis occurred. The case was further complicated by occlusion of the left brachial artery due to trauma associated with retrograde iodopyracet injection.

COMMENT

During the past decade a clearer understanding of the shoulder girdle syndromes has evolved. Although the symptoms and signs depend on which of the three important structures are involved, namely, the subclavian artery, the subclavian vein, and the brachial plexus, the mechanism of pressure and torsion may differ

from patient to patient, and a careful analysis is necessary to evaluate whether the difficulty is due to scalenus anticus pressure, with or without a cervical rib; or to the narrowing of the costoclavicular space, or, finally, to the hyperabduction syndrome. In any given case, more than one syndrome may be operative. Conservative therapy suffices to alleviate the symptoms in the majority of patients, but in some, surgical intervention is necessary. A new operative approach is presented which may prove to be of value in that it serves to correct all the anatomical and postural bottlenecks to the vital structures involved. The operation consists in total claviculectomy, complete removal of the periosteum, division of the scalenus anticus muscle, and mobilization of the subclavian artery downward. The results have been considered excellent in five patients, good in three, and fair in one. At present we believe that the operation is urgently indicated in patients who show frank arterial thrombosis and should be employed in patients without arterial thrombosis who fail to respond to a thorough trial with conservative measures. The cosmetic and functional results are good, and the period of disability postoperatively has usually been less than one month. A larger series of patients followed for a longer period of time will be necessary before final evaluation of the operation described herein can be made.

55 East 92nd St.

ABSTRACT OF DISCUSSION

Dr. Ross Veal, Washington, D. C.: I have not had any experience with this procedure, as described by Dr. Lord. I rise to bring up two points. One is that we have found the scalenotomy alone to be inadequate. In our experience the cervical rib provided the tie in; consequently, we feel that by the removal of the cervical rib, the anterior approach is quite satisfactory. Since we have all the structures exposed, this attack is completely adequate.

We made some studies some years ago trying to determine the anatomical influence by raising the arm on the axillary subclavian vein in relation to efferent thrombosis. At that time we made a series of studies, using the branches of the subclavian with the arm in different positions. We were unable to find any point of constriction in hyperabduction or in external rotation of the arm. We do know that the position of hyperabduction and external rotation occluded the axillary vein, and with the arm in that position we made a study of the venous flow in the subclavian vein. We did find that under severe respiratory pressure there was a tremendous pressure in the axillary vein, and unusual respiratory distress might cause some pressure on the valves to those veins. Dr. Lord, did you find hyperabduction of the axillary vein under the head of the humerus? I wonder if by removing the clavicle and delivering the vessel through, it might be removed. I should like to ask Dr. Lord if he does his removal by removal of the clavicle.

Dr. Harris B. Shumacker, Jr., Indianapolis: Dr. Lord has presented an intriguing method for dealing with intractable cases of the costoclavicular syndrome. Unfortunately, I have had no personal experience with his operation. Though, at first glance, the absence of significant functional impairment following removal of the clavicle may seem surprising, there are other experiences which might have led one to predict that this structure could be sacrificed without real disability. It has been common practice to excise long segments of the clavicle subperiosteally in order to provide adequate exposure of the brachial plexus or of the subclavian and axillary vessels. During the long period before osteogenesis occurs in the resected segment, the patient has little or no functional disturbance. Furthermore, in cases of cleidocranial dysostosis the affected patients have notably little dysfunction even though they are born without a clavicle.

Dr. Lord has properly emphasized the fact that the radical operative procedure he describes is one which has only a limited applicability in the treatment of the shoulder girdle syndromes as a whole. Certainly, of paramount importance is accuracy of diagnosis, trial of any promising nonoperative measures before resorting to surgical treatment and use of simpler specific surgical

procedures, when indicated, before carrying out more complicated and destructive operations. My own experiences with the treatment of the scalenus anticus and medius syndrome have been altogether rather good, perhaps because I have been more exacting, with regard to the fulfillment of definite diagnostic criteria, than some who have performed more scalenotomies with a higher percentage of unsatisfactory results. If one encounters a situation in which the costoclavicular space obviously must be widened, the bony bridge on one side or the other must be removed. It would seem that Dr. Lord's method of excising the overlying clavicle would be safer and easier than the excision with its periosteum of the underlying first rib.

Dr. Alexander Blain III, Detroit: Satisfactory surgical management of all the shoulder girdle syndromes requires good preoperative study and diagnosis. Often this is difficult. Of the last 10 patients seen at the Alexander Blain Hospital in whom the initial impression was that of the Naffziger syndrome, 5, or 50%, were found on further study to have cervical disc disease. We have found it of help in all cases which are not completely classic to enlist the aid of our neurosurgeons to rule in or out the very definite possibility of a ruptured cervical disc. Cervical disc disease and cervical arthritis must be ruled out, particularly when neurologic manifestations are more prominent than the vascular component.

My second point is that in patients with Raynaud's disease or Raynaud's syndrome, Adson's vascular test should be performed routinely. I have seen two patients subjected to preganglionic dorsal sympathectomy for a mistaken diagnosis of Raynaud's disease, without relief. Subsequent scalenotomy produced a cure in each case because in each case there was a scalenus anticus syndrome, which was the cause of Raynaud's syndrome. Aneurysmal dilatations should be searched for in all cases of constriction of the subclavian artery. These sometimes arise distal to the point of constriction produced by the scalenus anticus muscle and the first rib or a cervical rib when present. They have even been seen distal to an area of constriction at the insertion of the pectoralis minor. In all cases of subclavian aneurysm, scalenus anticus compression should be ruled out as the cause.

Many cases of thrombosis of the axillary or subclavian vein, the so-called effort syndrome, are probably due to compression by the scalenus anticus muscle. It has been my experience that when a cervical rib is present it should be resected. I have torn the pleura in a third of the cases in which I resected a cervical rib, but there has been no morbidity.

Finally, it should be emphasized that there are many other causes of block of the subclavian artery, including pressure from a traumatic hematoma arising from torn branches of the vein to the subclavius muscle. In the clear-cut scalenus anticus syndrome, with or without the cervical rib, anterior scalenotomy, with resection of the cervical rib if present, will be followed by uniformly good results, and resection of the clavicle would seem unnecessary. However, in the many cases which are not clear cut, the Lord operation appears to be a logical step in improving results for the patient and in adding to our rather primitive knowledge of the shoulder girdle syndromes in general.

Dr. Jere W. Lord, Jr., New York: I certainly appreciate the important points which the discussers have made and should like to make a few remarks about these observations.

It has been my unfortunate experience in holding retractors during an operation for scalenus anticus syndrome with a large cervical rib, which was done in two stages, that in some patients a neuritis may develop which is almost as bad as the original disease, and too many of them do not recover from it. I don't know how often that is a complication of a cervical rib. We tried to make room anterior to it, and not having to disturb the important structures of the brachial plexus may be simpler for the patient. As Dr. Shumacker brought out, a cervical rib is always a potential hazard.

Next is the point about the axillary vein, which Dr. Veal brought up. Two of the patients have had axillary venous thrombosis, but I am unable to say whether the improvement was due to the operation, or whether nature was taking care of that with the passage of time.

In answer to Dr. Blain's remarks regarding arthritis and the cervical disc, we have studied the arterial syndromes and have avoided the neurological-type patient. I do think that one has to be certain of the diagnosis and that one is not dealing with a lesion in the region of the cervical vertebra. The conditions of the two patients with Raynaud's disease have been unchanged. It may just be good luck, Dr. Blain, that they were helped by section of the scalenus anticus muscle. One patient had a small subclavian aneurysm distally, and we let it alone to see what the aneurysm would do. It has not enlarged.

NEW CONCEPT OF VESICAL INNERVATION

Relationship of Vesical Innervation to Bladder Management Following Abdominoperineal Proctosigmoidectomy

LOWRAIN E. McCREA, M.D.
AND
DONALD L. KIMMEL, Ph.D.
PHILADELPHIA

VESICAL dysfunction following some types of lower abdominal or pelvic surgery is known to occur occasionally. It is believed that this dysfunction is of neurogenic origin. In 1946 a theory of the causative factors of vesical dysfunction following abdominoperineal proctosigmoidectomy was presented.[1] At that time it was stated that such dysfunction was believed to be of neurogenic origin and resulted from excision of the inferior hypogastric and pelvic plexuses; that the bladder responded as if a sympathetic nerve predominance existed; and that the return of bladder function was due to nerve regeneration. Many of these statements have been proved to be incorrect. It is still believed that vesical dysfunction following abdominoperineal proctosigmoidectomy is of neurogenic origin. However, in the interim since the previous report, basic research on the innervation of the bladder has been done. Through the medium of this research, it has been demonstrated that nerve fibers accessory to those passing through the pelvic plexus are present and that they are also distributed to the urinary bladder (Figs. 1, 2, 3, 4, and 5).[2]

The demonstration of the accessory nerve supply to the bladder was accomplished by the study of serial sections of human fetuses. These findings have been further substantiated by gross dissection of stillborn infants and in the adult. These nerves, coursing to the bladder by a perivascular route in the endopelvic fascia within the bony framework of the pelvis, may be readily demonstrated (Fig. 6).

This study was supported by a grant from Hoffmann-LaRoche, Inc.

Read before the Section on Urology at the One Hundred and First Annual Session of the American Medical Association, Chicago, June 11, 1952.

From the Departments of Urology (Dr. McCrea, Clinical Professor) and Anatomy (Dr. Kimmel, Professor), Temple University School of Medicine and Temple University Hospital.

1. Bacon, H. E., and McCrea, L. E.: Abdominoperineal Proctosigmoidectomy for Rectal Cancer: The Management of Associated Vesical Dysfunction, J. A. M. A. **134**:523, 1947.

2. McCrea, L. E.: Management of Vesical Dysfunction in Anorectal Disease, Proc. Proctol. Soc., 1946; Management of Vesical Dysfunction Following Abdominoperineal Proctosigmoidectomy, J. Internat. Coll. Surgeons **10**:629, 1947. McCrea, L. E., and Kimmel, D. L.: The Importance of Nerve Supply of the Urinary Bladder in Surgery of the Rectosigmoid, read at the Assembly of the U. S. Chapter of the International College of Surgeons, Sept. 1951.

The usually described innervation to the bladder is considered by Learmonth [3] to arise from three sources. These three sources are the somatic, sympathetic and parasympathetic (Fig. 7).

The somatic innervation is supplied through the pudendal nerve, usually derived from the third and fourth sacral nerves. The distribution of this nerve is to the external sphincter, the striated muscle around the urethra.

It is through this nerve that the only volitional impulses of urination are carried.

The sympathetic fibers which innervate the bladder are given off the thoracolumbar outflow from the first and second lumbar segments and, possibly, from the twelfth thoracic segment. The sympathetic fibers to the bladder and other pelvic

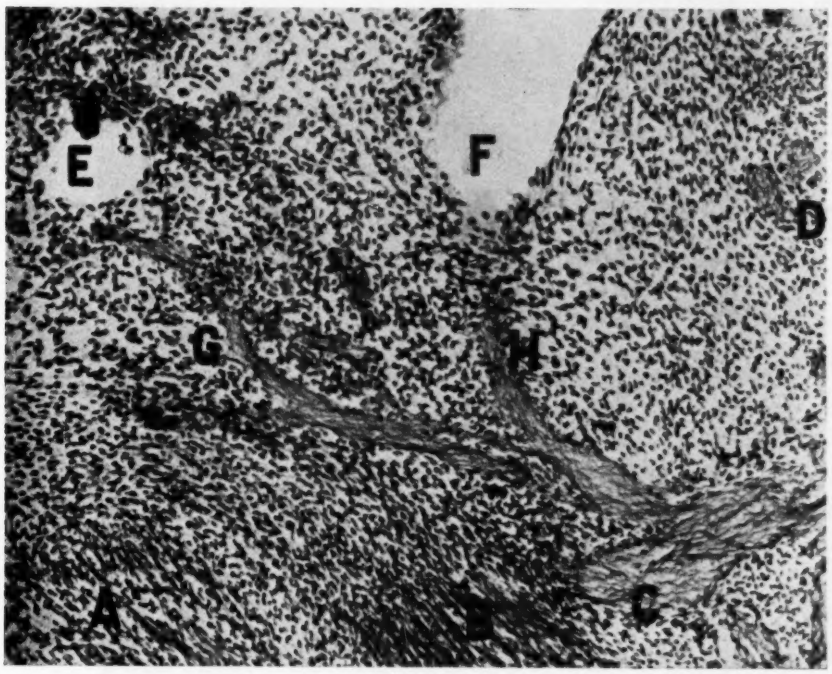


Fig. 1 (Section E723-2-1).—Sagittal section through lateral pelvic wall of a 20-mm. human embryo, showing course of visceral pelvic nerve branches to urinary bladder. In figure, dorsal is to right and cephalad toward top of photograph. *A*, levator ani muscle; *B*, coccygeus muscle; *C*, pudendal nerve; *D*, rami communicantes from sympathetic trunk; *E*, vesical veins which are tributaries to the anterior hypogastric vein; *F*, *G*, and *H*, visceral nerve branches from second, third, and fourth sacral nerves, coursing toward bladder within lateral layers of endopelvic fascia. Branch *G* can be followed in series to posterolateral wall of urinary bladder. Branch *H* ascends in perivascular position about hypogastric veins to level of convexity of ureter. From this level, nerve accompanies ureter to dorsolateral wall of urinary bladder. Silver stain; × 155.

viscera are finally concentrated in a strand called the presacral nerve. At the promontory of the sacrum the presacral nerve divides into the two hypogastric nerves, which join the posterior superior angles of the corresponding hypogastric

3. Learmonth, quoted by Langworthy, O. R.; Kolb, L. C., and Lewis, L. G.: Physiology of Micturition: Experimental and Clinical Studies with Suggestions as to Diagnosis and Treatment, Baltimore, Williams & Wilkins Company, 1940.

ganglia or pelvic plexus. From here, fibers pass onward to innervate the trigone, including the muscles of Bell and the muscles of the crista of the urethra.

The parasympathetic fibers arise from the second, third, and fourth sacral segments of the spinal cord and run through the pelvic plexus, which lies on the lateral surface of the rectum, to the bladder musculature.

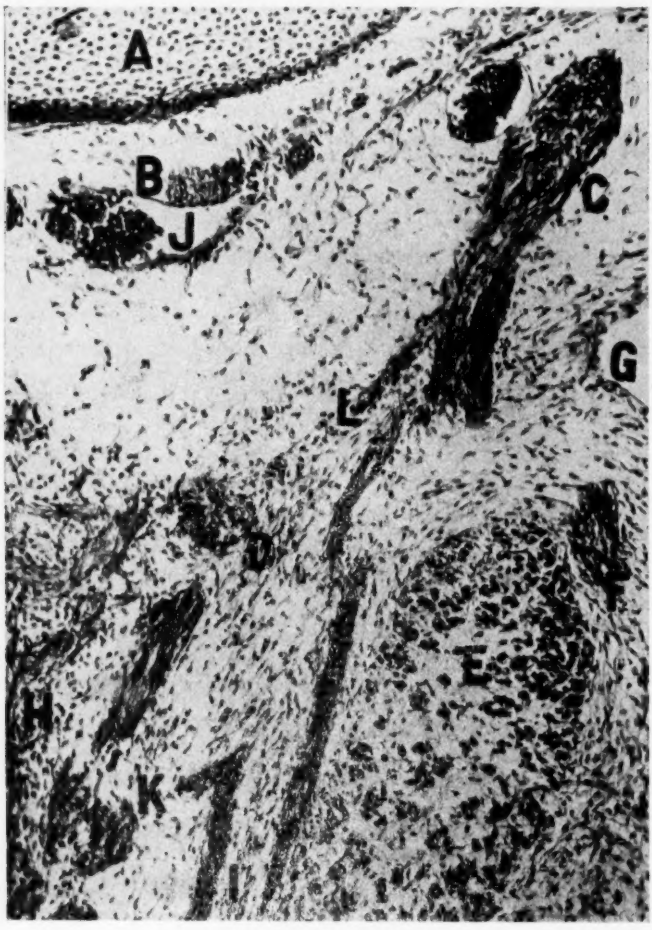


Fig. 2 (Section EI-15-1-3).—Transverse section through pelvis of 28-mm. human embryo at level of third sacral nerve. In illustration, dorsal is above, and lateral is to right. *A*, fourth sacral vertebra; *B*, sympathetic trunk; *C*, third sacral nerve; *D*, fourth sacral nerve; *E*, coccygeus muscle; *F*, pudendal nerve; *G*, internal pudendal vein; *H*, pelvic plexus; *I*, nerves to levator ani muscle; *J*, lateral sacral vein; *K* and *L*, visceral branches from third and fourth sacral nerves. Visceral nerves *K* and *L* leave loop formed by anterior divisions of third and fourth sacral nerves and enter pelvic plexus. Part of these fibers reach pelvic plexus as component of nerve to levator ani. Other fibers from third and fourth sacral nerves ascend from this level to become perivascular in position at junction of lateral sacral and internal pudendal vessels. These are shown in Figure 3. Silver stain; × 150.

If the bladder was supplied only by fibers which pass through the pelvic plexus, it would be without innervation and without stimulation to cause emptying after certain types of surgery, particularly abdominoperineal proctosigmoidectomy.

It is believed that the newly demonstrated accessory nerves aid and possibly take over completely the innervation of the bladder. The nerve bundles are given off

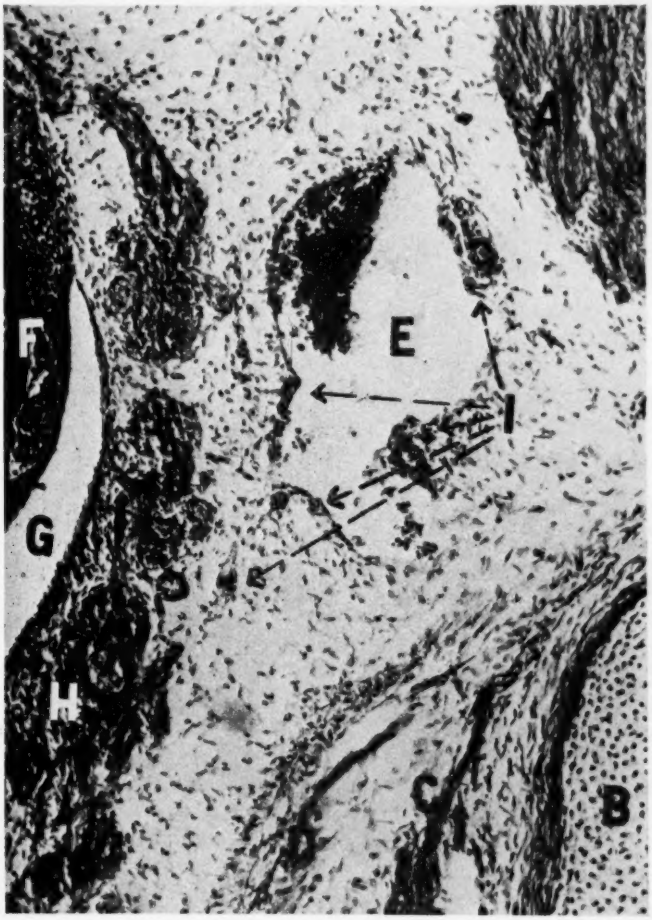


Fig. 3 (Section EI-23-2-3).—Transverse section through pelvis of a 28-mm. human embryo at level of exit of sciatic nerve through greater sciatic foramen. In photograph, dorsal is above and lateral is to right. *A*, sciatic nerve; *B*, ischium; *C*, obturator internus muscle; *D*, levator ani muscle; *E*, anterior division of hypogastric vein surrounded by several visceral branches (1) of sacral nerves; *F*, rectal wall; *G*, peritoneal cavity; *H*, pelvic plexus. Note nerves coursing anteriorly from their perivascular position about hypogastric vein to join anterior part of pelvic plexus. These fibers are distributed to prostatic and vesical plexuses. Note also that these nerve bundles join pelvic plexus laterally and anteriorly to peritoneal cavity. This relation is maintained in the adult. Nerves on anterior wall of vein are similarly distributed to the bladder at slightly higher levels. Those on lateral wall of vein ascend in their perivascular position to level of convexity of ureter. From here they accompany ureter to bladder wall and are distributed to detrusor muscle. Silver stain; × 150.

from the second, third, and fourth sacral roots (Fig. 8). They course in a perivascular manner along the veins on the lateral walls of the pelvis to enter the bladder at the level of the insertion of the ureters. It has been demonstrated that some of the fibers join the anterior part of the pelvic plexus interrelating the two nerve routes to the bladder. Nerves occupying a similar position are indicated in the figures

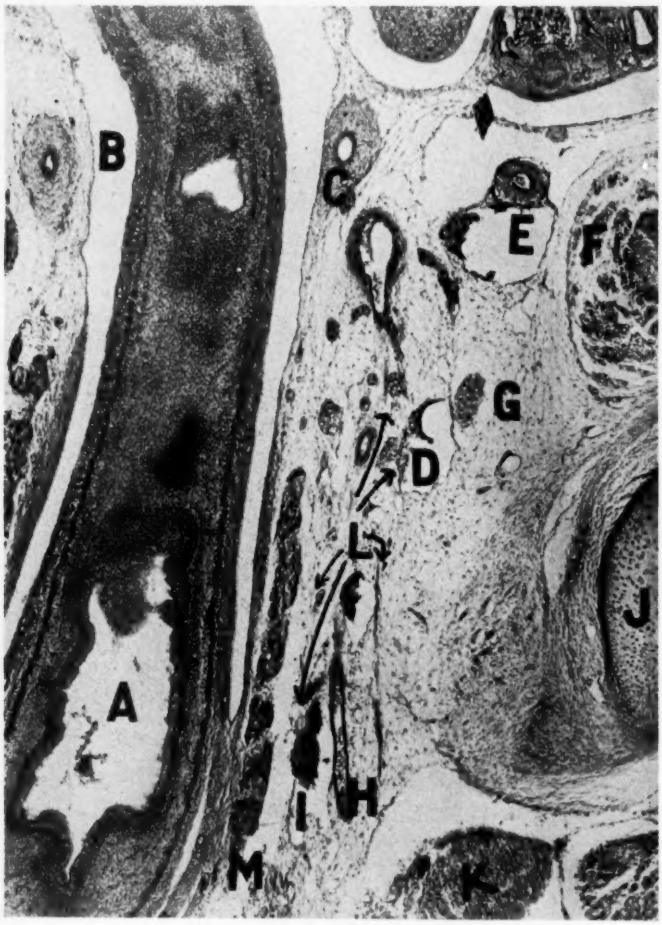


Fig. 4 (Section E17-143-1).—Frontal section through posterior aspect of pelvis of 33-mm. human embryo, showing laterality of position in endopelvic fascia of visceral nerves supplying ureter and bladder musculature. *A*, sigmoid colon and rectum; *B*, peritoneal cavity; *C*, ureter with ganglion on its inferior periphery; *D*, anterior division of hypogastric vein; *E*, external iliac vessels; *F*, psoas muscle; *G*, obturator nerve; *H*, internal pudendal artery; *I*, internal pudendal vein; *J*, ischium; *K*, sciatic nerve; *L*, visceral branches from second, third, and fourth sacral nerves; *M*, pelvic plexus. Note how visceral nerve bundles parallel branches of hypogastric vessels as nerves course through endopelvic fascia. Visceral nerves shown in upper part of photograph reach bladder independently of pelvic plexus. Others shown in lower part of figure join pelvic plexus anteriorly to rectum and at a position where pelvic plexus is separated from rectal wall by peritoneal cavity. Silver stain, counterstained with acroflavine; × 30.

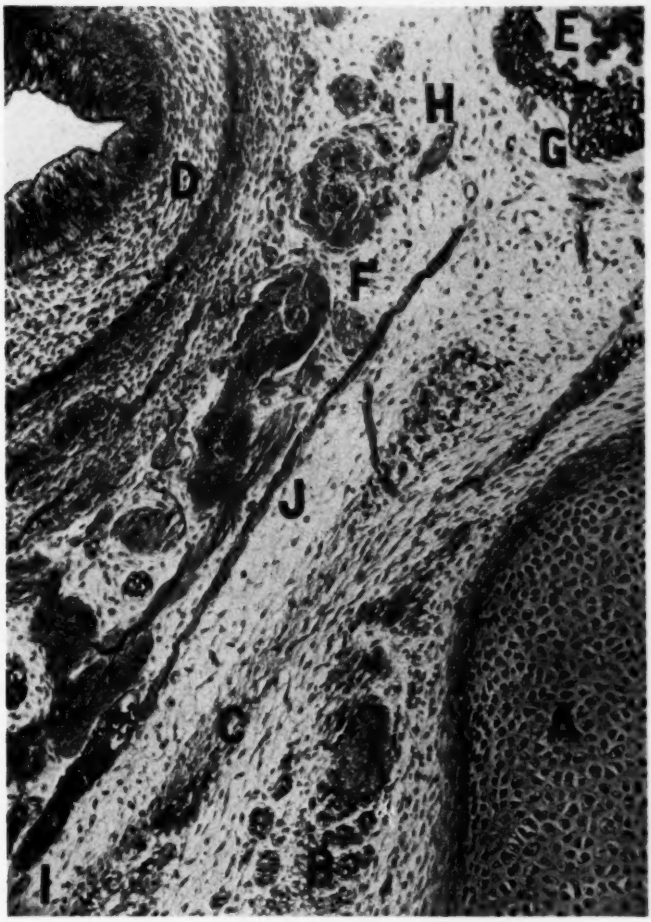


Fig. 5 (Section E33-285-3-5).—Transverse section through the posterolateral region of the pelvis of 33-mm. human embryo. *A*, ischium; *B*, obturator internus muscle; *C*, levator ani muscle; *D*, rectal wall; *E*, anterior division of hypogastric vein; *F*, pelvic plexus; *G*, *H*, *I* and *J*, visceral branches of third and fourth sacral nerves. Note position lateral to main mass of pelvic plexus of nerves *I* and *J*. These nerves are distributed to trigone, prostate, and urethra completely independently of pelvic plexus. Others, as represented by *G*, course rostrally along hypogastric vessels for a short distance, unite with contributions from second sacral nerve, and then turn anteriorly to reach bladder. Bundle of fibers labeled *H* is representative of sacral visceral branches which join pelvic plexus. Such nerves follow usually described route to bladder and rectum. Silver stain, counterstained with acroflavine; × 140.

described by Curtis, Anson, Ashley, and Jones (1942).[4] Pernkoff (1943) [5] clearly demonstrates these nerves in their course to the bladder. His illustrations, since based upon gross dissections, fail to show a representative number of the nerves lateral to the pudendal venous plexus. The pattern of distribution of the newly described nerves is such as completely to overlap the distribution of the fibers which reach the bladder through the pelvic plexus.

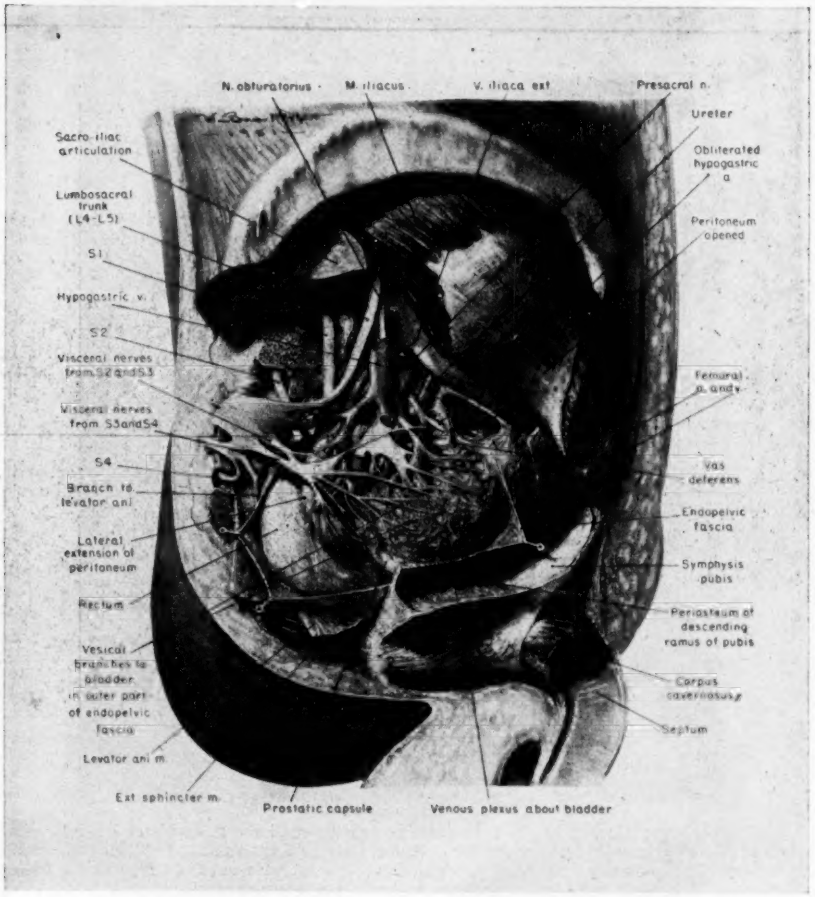


Fig. 6.—Dissection, showing parasympathetic nerves to urinary bladder.

It has been further found that there are ganglia located along these nerves as they course to the bladder, which indicates that some of the fibers might be of a

4. Curtis, A. H.; Anson, B. J.; Ashley, F. L., and Jones, T.: The Anatomy of the Pelvic Autonomic Nerves in Relation to Gynecology, Surg., Gynec. & Obst. **75**:743, 1942.

5. Pernkopf, E.: Topographische Anatomie des Menschen: Lehrbuch und Atlas der regionär-stratigraphischen Präparation; Band II: Bauch, Becken und Beckengliedmasse, Berlin, Urban & Schwarzenberg, 1943.

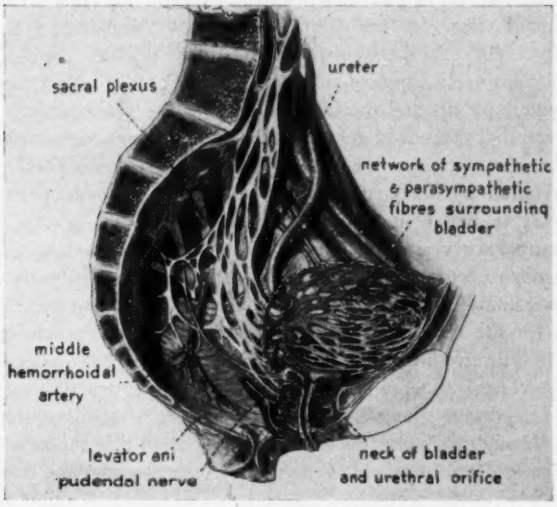


Fig. 7.—Parasympathetic nerves seen to enter inferior hypogastric or pelvic plexus together with sympathetic fibers. Pudendal nerve is in normal position and is not in direct communication with other nerve factors that control urination.

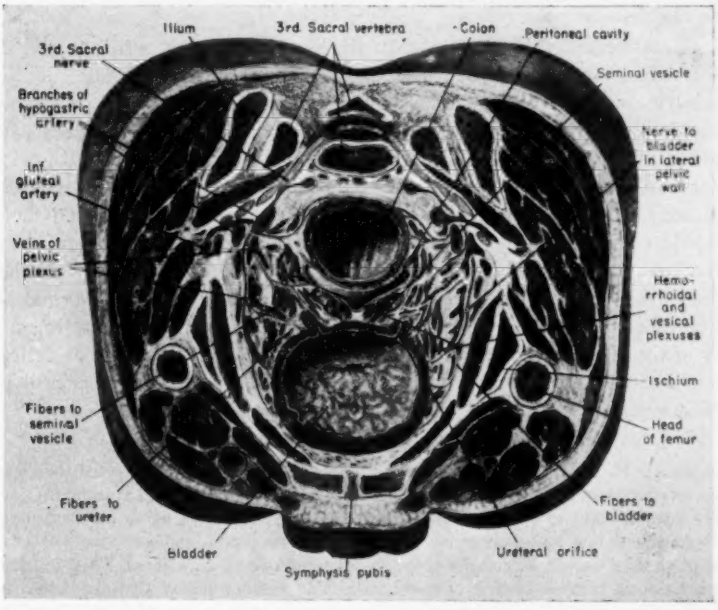


Fig. 8.—Cross section through pelvis of a man, showing position of nerves to urinary bladder as they course through endopelvic fascia. Note particularly relationship of nerves to blood vessels and their lateral position in endopelvic fascia.

parasympathetic nature. Upon stimulation they should cause relaxation of the internal sphincter and contraction of the detrusor muscle. Sympathetic nerve fibers also travel along the perivascular route to the bladder. Such being the case, the bladder is completely supplied with two separate and distinct innervations, one through the pelvic plexus and the other by way of the perivascular route.

It is believed that the newly described accessory nerves completely take over the function of the innervation of the bladder when the posterior portion of the pelvic plexus is disrupted by such surgical procedures as abdominoperineal proctosigmoidectomy. It is not believed that vesical dysfunction is due to obstructive uropathy. Temporary vesical atonia (based on the cystometrogram on the 10th postoperative day) occurred in 41 instances, or 6.9%, in 586 patients undergoing "proctosigmoidectomy." [6] The atonia occurred equally in women and in men. Prostatic surgery, for the relief of urinary retention following "proctosigmoidectomy," was required in only five instances in our series extending over a period of 12 years.

Temporary vesical atonia is considered to be due to traction on or trauma to the nerve fibers coursing along the perivascular route after disruption of the nerve fibers passing through the pelvic plexus. It is suggested that the incidence of vesical atonia would be less than it is now if sharp dissection, as near the bowel as possible, were done in freeing the rectum. Dissection should also be done as far away as possible from the base of the bladder when the bowel is mobilized. Permanent vesical atonia would occur after severance of all the nerves to the urinary bladder but would be of unusual occurrence.

CONCLUSIONS

It is established that nerves reach the bladder by two separate and distinct routes. These routes are (1) the established pathways through the inferior hypogastric or pelvic plexus and (2) the newly described pathways coursing to the bladder by a perivascular route. The nerves of the newly described pathways are given off from the second, third, and fourth sacral roots and course to the bladder along the blood vessels in the endopelvic fascia within the lateral walls of the bony pelvis. Many of these nerves run to their termination on the ureter and bladder independently of the pelvic plexus. Others join the pelvic plexus anteriorly to the rectum, in the lateral wall of the rectovesical fossa. It is believed that the presence of these nerves in their lateral position explains normal bladder function following removal of the rectum. It is believed that trauma to the nerve supply of the bladder, rather than obstructive uropathy, is the cause of vesical dysfunction following extended pelvic surgery, particularly abdominoperineal proctosigmoidectomy.

ABSTRACT OF DISCUSSION

Dr. Joseph H. Kiefer, Chicago: Drs. McCrea and Kimmel have presented the conclusions of their investigations into the problem of urinary dysfunction after rectal resection.

They have brought to our attention the presence of perivascular nerve bundles surrounding the hypogastric vessels and their branches. They postulate for those fibers functions other than control of vascular tone, which is the presently accepted role of such fibers. They feel that these fibers can assume nervous control of micturition. The authors believe that the disturbances of bladder function which follow rectal surgery are entirely neurologic and that mechanical obstruction plays no part whatsoever, recovery resulting from assumption of nervous control by the perivascular nerve fibers.

6. Seen on the Proctologic Service of Dr. Harry E. Bacon, Temple University Hospital.

Our own experience has been otherwise. Mechanical obstruction has played a very definite role in those patients we have seen. The patients we are called to see are those who have been unable to void reasonably well on removal of the indwelling catheter, which is routinely placed at the time of rectal resection. This group has amounted to about 5 to 10% of men undergoing operations. Urologic examination of these patients has, in all but a few cases, revealed cystoscopic evidence of vesical neck obstruction of a mechanical nature. Surgical correction by transurethral resection has given excellent results, even in those cases in which the disability was out of proportion to the evident obstruction.

We feel the problem cannot be simplified to a purely neurologic or purely mechanical one. It is by nature complex, and all etiologic factors demand consideration.

Those who must undergo this operation are from the age group in which a considerable number of vesical neck obstructive lesions occur, although many are still subclinical. Is it surprising that surgery should precipitate complete retention in some of these cases, when such minor derelictions as alcoholic or sexual indulgence or voluntary retention will do the same thing?

Add the direct trauma to the bladder and urethra during surgery, the disturbance to mechanical supports and anatomic relationships, and then to this add the neurologic disturbances.

The neurologic effects are not all due to direct injury to nerve pathways, such as division, stretching, or avulsion. Many of the early neurologic effects are undoubtedly reflex, and we might well expect them, since a hemorrhoidectomy or simple hernia operation can cause a reflex retention in a normal bladder. Early recovery from such effects may well be expected; so development of alternate reflex pathways is necessary.

When damage has been done to the pelvic ganglia and to the adjacent nervous structures, the development of alternate pathways for reflex activity and central control would certainly make recovery more rapid and complete. But only when there has been complete bilateral destruction of the normal connections would it be necessary to postulate new pathways, since it has been shown that unilateral destruction does not destroy central control.

Our personal experience has been that when persistent disability occurred, there was usually mechanical obstruction present, and relief was obtained by transurethral resection.

The suggestion of close dissection to the rectum to avert nerve damage is not acceptable to many surgeons who feel that this procedure will increase the risk of leaving behind involved tissue and nodes and is therefore undesirable.

RELATIONSHIP BETWEEN BENIGN BREAST DISEASE AND CANCER

EDWARD F. LEWISON, M.D.
BALTIMORE
AND
JOHN G. LYONS Jr., M.D.
HARTFORD, CONN.

MODERN medical vigilance and early cancer detection require an accurate appraisal of the importance of benign breast disease and its relation to cancer. The strength of such a study rests upon the weakness of our present modes of cancer diagnosis and therapy. Does the significance of chronic cystic mastitis lie in the insignificance with which it is so often regarded? Should patients with fibroadenosis look forward to the future as a promise or as a threat? Can we accept with confidence the vacillating voices of preeminence, or must we fall back upon ill-defined and intangible clinical judgment, the limitations of which are all too apparent in the candor of our own individual experience?

Each of us I am sure can recall a patient operated upon for a benign breast lesion, verified as innocent by pathologic examination, in whom some time later a carcinoma developed within the operative site. Or many of us at least must certainly remember a patient with a small lump in her breast known to have been present for 10 to 20 years before an increase in size compelled its removal for unforeseen cancer. These striking examples of anatomic relationship might seem to be a link that is "a little more than kin and a little less than kind." Yet one must be extremely cautious in deriving probabilities based upon the principles of individual clinical impressions. The pitfall of this error lies within the very shadow of truth.

The importance of determining the relationship between benign and malignant breast disease is accentuated by the present challenge of a constantly increasing toll of breast cancer. This is considerably greater today than it was a generation ago. Recently, the National Cancer Institute estimated that the number of new cancer cases (all sites) increased 34% during the 10-year period 1937 to 1947 and, of this, only 7% could be accounted for by the increase in life span of the population. Thus, although our accumulated knowledge of breast cancer is formidable, we have by far the greater part of its conquest yet to attain.

From the Breast Clinic, Division of the Tumor Clinic, Department of Surgery, the Johns Hopkins Hospital, Baltimore.

This paper was presented at the Sectional Meeting of the American College of Surgeons, Atlantic City, N. J., Feb. 11, 1952.

This investigation was supported in part by research grants from the S. Kann Sons Foundation, the Alexander and Selma H. Hecht Foundation, and the Marcelle Fleischmann Foundation (through the Maryland Division of the American Cancer Society).

HISTORICAL REVIEW

Among the earliest known records of surgical antiquity, the Edwin Smith papyrus (C. 1600 B. C.)[1] unmistakably defines the "hard and cool swellings of the breast" so characteristic of cancer. These tumors for which "there is no treatment" were clearly differentiated from breast abscess and inflammatory mastitis. However, the distinction between benign breast disease and cancer escaped recognition until the revelations of microscopic anatomy in the 19th century.

As noted by Goodall,[2] Honorary Librarian of the Glasgow Royal Faculty of Physicians and Surgeons, in his carefully documented history of fibroadenosis, the early Greek physicians, in spite of their keen observation of clinical syndromes left no record of their knowledge of benign breast disease. Concerning occult (non-ulcerated) cancer, the aphorisms attributed to the Father of Medicine, Hippocrates (460 to 370 B. C.),[3] advised: "It is better to omit treatment altogether; for, if

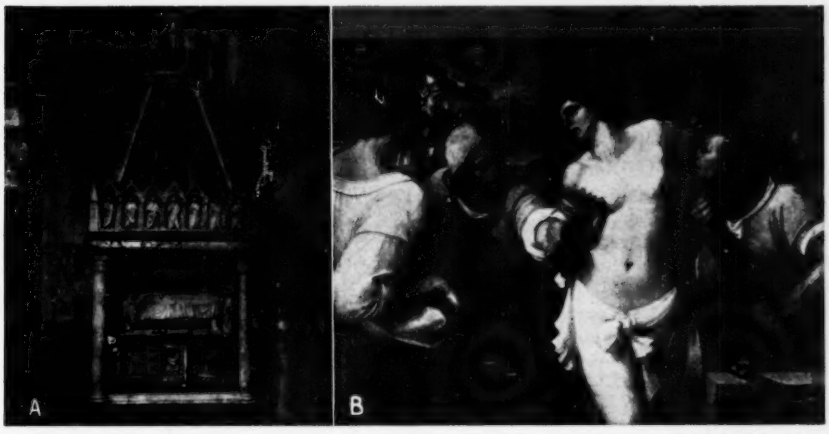


Fig. 1.—*A*, shrine of St. Agatha in Verona Cathedral, Italy. *B*, martyrdom of St. Agatha, patron saint of diseases of the breast.

treated, the patients soon die, whereas if let alone, they may last a long time." Galen (131-201 A. D.)[4] with characteristic didactic conviction, asserted that "cancerous tumors are found in all parts of the body, but particularly in the breasts of women, after the cessation of menstruation, which, so long as it is regular, preserves good health." The shrine of St. Agatha[5] (Fig. 1, *A* and *B*), the patron saint of

1. Breasted, J. H.: The Edwin Smith Surgical Papyrus: In Facsimile and Hieroglyphic Transliteration, with Translation and Commentary, Chicago, University of Chicago Press, 1930, Vol. 1, Case 45, pp. 403, and 463.

2. Goodall, A. L.: The History of Fibroadenosis of the Breast, Bull. Hist. Med. **25**:226-235, 1951.

3. Hippocrates, with an English translation by W. H. S. Jones, London, Putnam & Co., Ltd., 1923, Vol. 4, p. 189, Aphorism 6, No. 38.

4. Galen, C.: Opera Omnia, Editionem Curavit Carolus Gottlob. Kühn, Lipsiae, Cnobloch, 1821-1833, Vol. 11, p. 139.

5. Lewison, E. F.: Saint Agatha the Patron Saint of Diseases of the Breast, Bull. Hist. Med. **24**:409-420, 1950.

breast diseases whose martyrdom occurred in the third century A. D., offered solace and comfort to those afflicted with maladies of the breast.

Among the medieval, renaissance, and early modern surgeons and anatomists, Guy de Chauliac (1300 to 1368), Fabricius (1537 to 1619), Vesalius (1514 to 1564), and Ambroise Paré (1510 to 1590), one finds many original descriptive illustrations of breast anatomy and several rather clearly defined accounts of carcinoma and breast abscess, but the conception of benign breast tumors remained dormant. John Hunter (1728 to 1793),[6] a prolific writer, versatile surgeon and astute observer, recorded a giant fibroadenoma as a case of "scrofulous breast, which came on at the age of twenty-six, and increased gradually to thirty-eight. It was sixteen or eighteen pounds in weight. In this case there was no disease leading to the axilla, as in cancer." In Hunter's "Lectures on the Principles of Surgery," delivered in 1786 and 1787, he distinguished between scrofula in the form of a benign breast tumor and cancer:

> If cancer, it will vary its appearance by becoming less circumscribed, not having so determined an outline, from the cellular membrane around becoming diseased; the skin will be less movable, the nipple more or less retracted, and the lymphatic glands going to the axilla will swell. But in scrofula there will be no surrounding disease, no affection of the nipple or axillary glands, no adhesion, even though the tumor be large.

It was Abraham Colles (1773 to 1843),[7] a brilliant Irish surgeon of eponymic fame, who first clearly defined benign breast diseases in his "Treatise on Surgical Anatomy," in 1811:

> Although the diagnosis between scirrhus and other diseases of the breast be not founded on the anatomical structure of this part, and consequently does not come within the scope of this work, yet I cannot refrain from stating the symptoms of another species of tumor, which is occasionally met with in the breast, as it is not described by any other author I have hitherto seen.

An excellent clinical exposition follows which concludes with the hope "of preventing this kind of tumor from being mistaken for a true scirrhus."

Sir Astley Paston Cooper (1768 to 1841),[8] in his classic study "Illustrations of the Diseases of the Breast," published in 1829, divided breast lesions into three distinct classes: (1) common inflammation, acute and chronic; (2) complaints arising from peculiar or specific action, nonmalignant, and (3) malignant. Nonmalignant tumors were distinguished as

> . . . those which do not arise from a vitiated state of the system, nor produce any dangerous constitutional effects; and do not contaminate the parts in their neighbourhood, nor affect those at a distance from their original seat.
>
> However, it is right to observe that some of these swellings, when they have existed long in a dormant state, will have alterations produced in them by changes of the constitution, by which their extirpation may be rendered necessary; for malignancy may be lighted up in them by constitutional diseases . . . by anxiety of mind . . . and by the cessation of the menstrual secretion.

6. Hunter, J.: Lectures on the Principles of Surgery, in the Works of John Hunter, London, Longmans, Green & Co., Inc., 1835, Vol. 1, p. 618.

7. Colles, A.: A Treatise on Surgical Anatomy, Dublin, Gilbert and Hodges, 1811, p. 128.

8. Cooper, A. P.: Illustrations of the Diseases of the Breast, London, Longman, Rees & Co., 1829.

Later, in his introduction to "The Anatomy and Diseases of the Breast" (1849), Sir Astley Cooper [9] reviews the resemblance between nonmalignant and malignant "affections" and comments:

> These abnormal growths (non-malignant), although they might similate with such morbid changes in some of their characters and symptoms, yet differ from them (malignant) in their progress, in the treatment which they required, and in the probability of a fatal termination.

Velpeau (1795 to 1867),[10] a great teacher with opportunities for tremendous clinical experience, recorded his diligent observations in "A Treatise on the Diseases of the Breast and Mammary Region," which was published in 1854. In the differential diagnosis between cancer and innocent breast tumors, Velpeau comments on the transformation of tumors:

> If it were shown that cancer were only the ultimate state, the transformation of tumors originally innocent, a more minute examination, a more extended semiology would be useless; but as has already been seen, if the possibility of certain transformations cannot be denied, it is at any rate incontestable that they are rare.

In conflict with the prevailing views of Lisfranc, whose contrasting opinion maintained that every tumor of the breast led to cancer, Velpeau "laboured incessantly to remove from the category of cancers different tumors which do not belong to it."

Sir Benjamin Collins Brodie [11] in his "Lectures on Pathology and Surgery" (1846) regarded cystic tumors as benign but did not preclude the possibility of the development of carcinoma. He called attention to the recurrence of those multiple benign cysts if the entire mammary gland was not removed. In 1883 Reclus [12] made a comprehensive clinicopathologic study of "cystic disease of the breast," and his description of this syndrome is tenable today. He considered benign lesions as multiple, bilateral, not associated with cachexia or lymph node enlargement, nontender, smooth and without fixation, thus differing from malignant lesions. Since one can neither fortell nor prevent the possibility of cancer development in older patients with "cystic disease," Reclus recommended the removal of the diseased breast. The exhaustive histologic studies of Brissaud (1884)[13] attached great significance to epithelial proliferation. This served as a stimulus for similar cytologic investigations by Schimmelbusch (1890, 1892),[14] in Germany, which were rewarded by calling adenosis or adenoma with cyst formation, Schimmelbusch's disease, a most unwieldy and ponderous name. König (1893),[15] on the contrary, christened the lesion "chronic cystic mastitis" in the belief that epithelial proliferation and inflammatory interstitial changes were the result of a vicious cycle of secretion and irritation.

---

9. Cooper, A. P.: The Anatomy and Diseases of the Breast: To Which Are Added His Various Surgical Papers, Philadelphia, Lea & Blanchard, 1845.

10. Velpeau, A.: A Treatise on the Disease of the Breast and Mammary Region, translated from the French by M. Henry, London, Sydenham Society, 1856.

11. Brodie, B. C.: Lectures Illustrative of Various Subjects in Pathology and Surgery, London, Longmans, Green & Co., Inc., 1846.

12. Reclus, P.: La maladie kystique des mamelles, Rev. chir. **3**:761-775, 1883.

13. Brissaud, E.: Anatomie pathologique de la maladie kystique des mamelles, Arch. physiol. **3**:98-113, 1883.

14. Schimmelbusch, C.: Über das Cystadenom der weiblichen Milchedrüse, Verhandl. Deutsch. Gesellsch. Chir. **19**:116-120, 1890; Das Cystadenom der Mamma, Arch. klin. Chir. **44**:117-133, 1892.

15. König, F.: Mastitis Chronica Cystica (Interstitielle Mastitis, Cystadenoma mammæ, Maladie de Reclus etc.), Zentralbl. Chir. **20**:49-53, 1893.

Since so panoramic a study is contingent upon so many perplexing problems and so much doubtful data, there has accumulated a vast and still rather vague accounting of this clinicopathologic subject in the medical literature. Owing to this immense fecundity and prolixity of the press, reference can be made only to specific papers which seem most pertinent to the problem at present. The comprehensive resumés of Semb,[16] Campbell,[17] Foote and Stewart,[18] Cheatle and Cutler,[19] Patey,[20]

TABLE 1.—*Collective Review of the Relationship Between Benign Breast Disease and Cancer*

Author	Year of Publication	Type of Diagnosis	Total No. of Cases	% Followed	Follow-Up Period, Yr.	% of Cases Followed in Which Cancer Developed	Comment
Schimmelbusch	1890	Pathologic	43	..	None	7.0	Coexistence of cancer and benign breast disease
Speese (personal)	1910	Pathologic	35	..	None	26.0	Coexistence of cancer and benign breast disease
Speese (collected)	1910	Pathologic	295	..	None	15.0	Coexistence of cancer and benign breast disease
Greenough and Simmons	1914	Pathologic	102	81	1-17	4.8	59 patients out of 83 had partial resection and 32 patients had a local excision; average follow-up period 7 yr.
Bloodgood	1921	Pathologic	128	..	.....	2.4	Follow-up period and number of patients followed not stated
Johnson	1924-1925	Pathologic and clinical	107	61	1-20	1.9	Cystic disease alone considered
Semb	1928	Pathologic	144	..	None	17.0	Frequency of cancer in pathologic examination of primary fibro-adenomatosis
Oliver and Major	1934	.....	106	..	5+	1.0	.....
Campbell	1934	.....	190	62	5+	0.5	Simple cystic disease
Campbell	1934	.....	42	52	5+	0.0	Adenocystic disease
Klingenstein	1935	Pathologic	226	24	2-11	3.7	Patients upon whom only partial breast excision was done
Warren, I	1940	Pathologic	1,206	..	Average 9 yr.	3.5	Aggregate cases, including chronic mastitis, chronic cystic mastitis, cystadenomas, adenomas, in all cases
Warren, II	1940	Pathologic	604	67	Average 9+	4.9	Massachusetts cases alone, chronic mastitis, 173; chronic cystic mastitis, 340; cystadenomas, 21; adenomas, 70; cancer, 30
Warren, III	1940	Pathologic	602	..	5+ in ⅔ of cases	2.0	Toronto cases alone, chronic mastitis, 128; chronic cystic mastitis, 403; duct papilloma, 71; cancer, 12
McKinley	1943	Pathologic	60	47	1-10	0.0	Average follow-up period only 3 yr.
Clagett and co-workers	1944	Pathologic	442	86	5-6	1.8	Short term follow-up from Mayo Clinic
Geschickter	1948	Pathologic and clinical	793	..	5-30; average, 10+	1.3	Mastodynia 231, cancer in 0; adenosis 184, cancer in 6; cystic disease 378, cancer in 4
Atkins	1950	Pathologic and clinical	326	78	1-14	0.8	Material from Mastitis Clinic of Guy's Hospital, all cases called fibroadenosis
Present series	1951	Pathologic	451	85	1-25	1.8	Average follow-up period of 13.6 yr. with 75% of all patients being followed from 10 to 25 yr.

16. Semb, C.: Pathologico-Anatomical and Clinical Investigations of Fibro-Adenomatosis Cystica Mammae and Its Relation to Other Pathological Conditions in the Mamma, Especially Cancer, Acta chir. scandinav. (Supp. 10) **64**:1-484, 1928.

17. Campbell, O. J.: Relationship Between Cystic Disease of the Breast and Carcinoma, Arch. Surg. **28**:1001-1056, 1934.

18. Foote, F. W., and Stewart, F. W.: Comparative Studies of Cancerous Versus Non-cancerous Breasts, Ann. Surg. **121**:6-53, and 197-222, 1945.

19. Cheatle, G. L., and Cutler, M.: Tumors of the Breast: Their Pathology, Symptoms, Diagnosis and Treatment, J. B. Lippincott Company, Philadelphia, 1931.

20. Patey, D. H.: Chronic Cystic Mastitis and Carcinoma, Collective review, Internat. Abstr. Surg. **68**:575-579, 1939; in Surg., Gynec. & Obst., 1939.

Klingenstein,[21] and Warren [22] are authoritative compendiums of work and wisdom, past and present, which have nourished this branch of the tree of knowledge. That the current conception regarding the relationship between benign breast disease and cancer is dependent upon the most divergent data can best be seen by such statistical inconsistency as is summarized in Table 1.

MATERIAL

Definition.—In a study of benign breast disease it is often a desirable gambit to begin by defining one's terms. For no matter to what precision one may aspire, in a clinical investigation of benign breast lesions one is constantly handicapped by a barrier of conflicting and complicated terminology. Benign breast disease enfolds in its indiscriminate embrace a galaxy of "synonyms," all of which are in common use and many of which describe what may actually be the same lesion. Thus, we are often confronted with a potpourri of terms which include fibroadenosis, fibrocystic disease, chronic cystic mastitis, mastopathy, nodular hyperplasia, cyclomastopathy, adenofibromatosis, papillomatosis, Reclus' disease, Bloodgood's blue-domed cysts, Schimmelbusch's disease, mazoplasia, cystiphorous epithelial hyperplasia, chronic mastitis, mammary dysplasia, mastodynia, adenosis, adenocystic disease and several other complex and hybrid names. These are often repeated in the literature, thus adding chronicity to confusion.

Foote and Stewart [18] in their scholarly study of cancerous versus noncancerous breasts do not favor

> . . . the term "chronic cystic mastitis" in the diagnosis of lesions of the breast, since it conveys no indication of the presence or absence of many characteristic histopathologic changes; moreover, it implies a common etiology for a variety of lesions, most of which are anything but basically inflammatory processes.

However, they concede that

> . . . the term "chronic cystic mastitis" is so ingrained in the minds of some pathologists that this diagnosis of a locally excised portion of breast almost amounts to a surgico-pathologic reflex. Such haphazard terminology leads to neglect of the actual lesions, even though it may enforce the employment of a rather complicated terminology.

Nevertheless, the present opinion of American physicians is biased in favor of the term "chronic cystic mastitis" (in Great Britain the term "fibroadenosis" appears to be preferred). Although a term should not be considered correct merely because it is useful, yet chronic cystic mastitis is a byword of expediency because it is accepted by all, advocated by authority, and recommended by custom. For the purpose of this presentation we will risk the fallacy of oversimplification by using the term "benign breast disease" whenever possible. Where a less timid terminology is required we prefer (1) chronic cystic mastitis, the all-inclusive clinicopathologic complex with characteristic lesions of microscopic cysts; (2) fibroadenoma, the diffuse or localized proliferation predominantly of fibrous tissue, and (3) papilloma, the proliferation and papillary hyperplasia of epithelial elements. Ductal epithelium may reveal plication, layering and great cellular variability without nuclear changes characteristic of cancer.

---

21. Klingenstein, P.: Cystic Disease of the Breast, Ann. Surg. **101**:1144-1152, 1935.

22. Warren, S.: The Relation of "Chronic Mastitis" to Carcinoma of the Breast, Surg., Gynec. & Obst. **71**:257-273, 1940.

It is of great importance to point out that this classification is based upon the predominant pathologic picture in each individual patient. In many patients with benign breast disease the pathologic picture is representative in part of two or more types of abnormality. Rarely does the lesion consist entirely of a pure or single pathologic type. The routine practice of Cheatle and Cutler [19] of examining microscopic sections of whole breasts "definitely proves that it is unsafe to assume that sections made from only part of a breast represent the state of the whole gland."

Procedure of Present Study.—This investigation constitutes a long-term follow-up survey of all patients who were operated upon at the Johns Hopkins Hospital for benign breast disease during the period 1925 through 1941. Each patient was a hospitalized "bed patient," and the validity of the diagnosis was based upon pathologic evidence obtained in the operating room by use of the scalpel rather than by the random probing with an aspirating trochar. The thorns of our experience at the Breast Clinic have cautioned us against the peril of putting too much faith in the thin ice of clinical diagnoses alone. Credulity in unconfirmed clinical impressions has been the common failing of several otherwise reliable studies of a similar nature.

The diagnostic index of the hospital record room augmented in part by the daily operating room schedule and annual surgical pathology files were all consulted to render the statistics of this survey as trustworthy as possible. Patients with benign breast lesions who were operated upon in the outpatient department of this hospital —a practice no longer permitted—were not routinely indexed in the diagnostic files and therefore could not be included in this review. This may account for the seemingly modest total number of patients making up our study. Since most major uncertainties in medical statistics can be found in the selection of cases, it is necessary to acknowledge this preferential choice, but it is difficult to see how it could conceivably influence the validity of our results.

In clinicopathologic studies, which rely upon collected series of cases, there is always the inherent difficulty of a variable borderline in the histologic classification of benign and malignant breast tumors. It is quite likely that among competent surgical pathologists there is a marginal zone of differential diagnosis in which honest diversity of opinion exists. Although it may be difficult to define to the satisfaction of all pathologists the frontier between atypical hyperplasia and neoplasia, nevertheless, it is important to recognize the existence of such marginal zones. Even at an individual institution long steeped in the historic tradition and training of celebrated surgeons and surgical pathologists all keenly interested in the diseases of the breast, the expectation of a more uniform and exact standard of diagnosis and pathologic classification is not entirely fulfilled. The difficulty of diagnosis is well illustrated by Figures 2 *A* and *B*, as well as by the discussion and evaluation of this topic by Cheatle and Cutler,[19] Campbell,[17] and Bloodgood.[23] In 1931 Bloodgood [23] set forth a clinical dictum that is tempting if true. When the diagnosis of malignant growths can be made with ease, the course of the disease is characteristic of cancer. However, when the pathologic diagnosis is doubtful, the course of the disease is usually benign, regardless of the type of treatment.

23. Bloodgood, J. C.: Border-Line Breast Tumors, Ann. Surg. **93**:235-249, 1931.

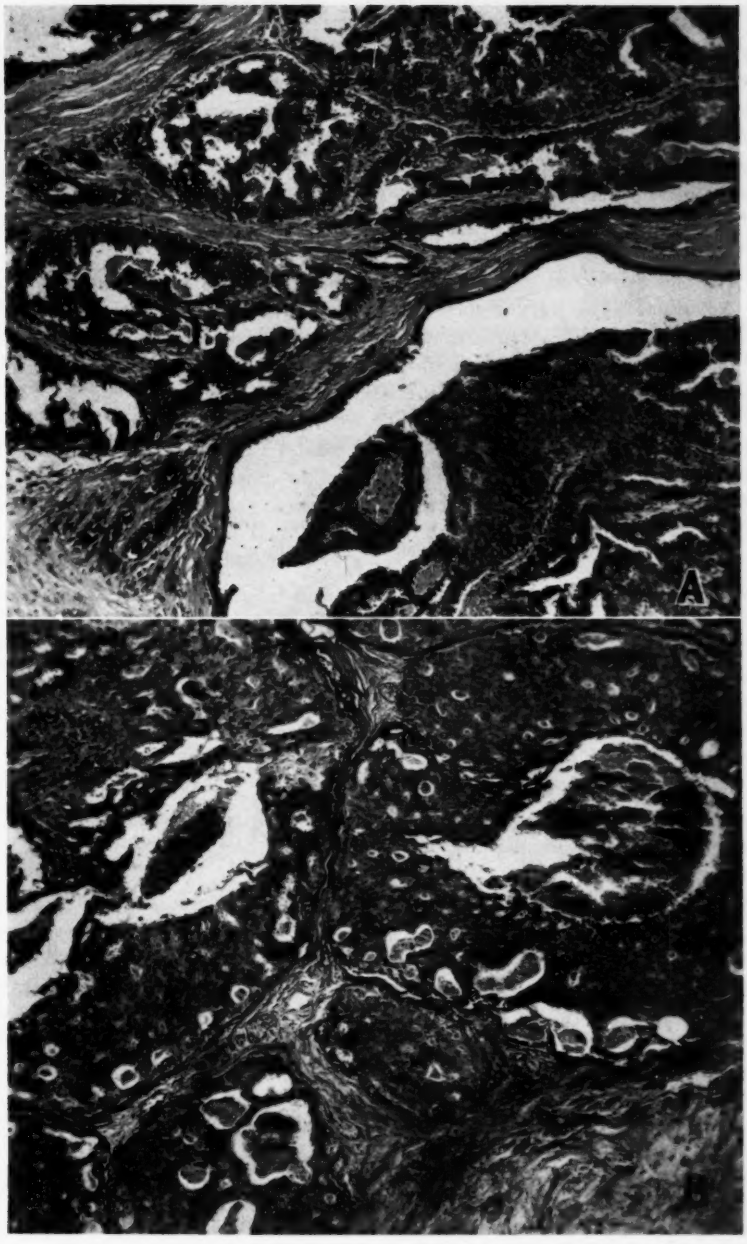


Fig. 2.—*A*, photomicrograph of borderline breast tumor removed by simple mastectomy at The Johns Hopkins Hospital in 1935 and diagnosed then and now as "benign intraductal papilloma"; × 100. Section reviewed by Dr. Arthur Purdy Stout, of New York; Dr. Fred W. Stewart, of New York; Dr. Lauren V. Ackerman, of St. Louis, and Dr. Hugh G. Grady and staff, of the Armed Forces Institute of Pathology, all of whom concurred in a diagnosis of carcinoma, papillary or comedo type. *B*, photomicrograph of recurrent breast tumor (in same patient) in operative scar, removed in 1951; × 100. All pathologists, including those of Baltimore, concurred in a diagnosis of carcinoma.

The inclusion or exclusion of these cases of borderline cancer is the bane of all accurate medical statistics. Some earlier reports concerning the curability of breast cancer have run aground on the shoals of such uncertain cases. Bloodgood [23] disclosed:

> The first case of Schimmelbusch's disease observed in the Johns Hopkins Hospital was operated on by Halsted for cancer in 1892, clearly described in the gross and microscopic picture by Welch, but the glands were not involved and the patient is living today, thirty-eight years after operation.

Halsted [24] himself noted that different surgeons and pathologists might "in perfectly honorable ways" vary in their diagnosis and treatment of breast lesions, thus providing a basic difference in cure rates. The pathologists on whom surgeons must rely "may classify as carcinoma the tumors which on microscopic examination show dangerous spots" but none of the classical characteristics of cancer.

Between 1925 and 1941 inclusive there were 451 patients operated upon at the Johns Hopkins Hospital for benign breast disease (Table 2). This period, ending in December, 1941, was especially chosen to allow most patients under survey to approach or actually reach the so-called cancer age. Obviously this latent period

TABLE 2.—*Comparison of Patients Followed with Patients Unable to Be Followed in the Present Series*

	Patients		Place of Residence				Status			
			Baltimore and Vicinity		Not Local		Private Patients		Clinic Patients	
	No.	%	No.	%	No.	%	No.	%	No.	%
Followed	385	85.4	237	62	148	38	135	35	250	65
Unable to be followed	66	14.6	24	36	42	64	34	52	32	48

alone has inevitably increased the difficulties of patient follow-up and consequently decreased the number of patients successfully followed. Nevertheless, a total of 385 patients were finally accounted for, thus completing an 85.4% follow-up over a 1- to 25-year survival span.[25]

We have been intentionally cautious in classifying clinical cases of alleged breast cancer as cancer unless this diagnosis could be verified by microscopic examination. In avoiding these small errors, which oftentimes lead to a grand fallacy, it is well to explain that two patients with breast cancer were deliberately deleted from this study. In one patient a breast tumor was removed, which was carefully examined and found to be benign. Three months later the patient was reoperated upon and carcinoma was found within the operative site. Axillary nodes contained cancer. By virtue of time alone this case appears to be open to question, and therefore we have considered the patient unsuitable for follow-up investigation. Time being the fourth dimension and the very essence in the evaluation of the relationship between benign breast disease and cancer, it seems improbable that so rapid

24. Halsted, W. S.: The Results of Radical Operations for the Cure of Carcinoma of the Breast, Ann. Surg. **46**:1-19, 1907.

25. The case-finding perseverance of Dr. John G. Lyons Jr. and Miss Marilyn Leavitt is acknowledged. ("Neither snow, nor rain, nor heat, nor night stays these couriers from the swift completion of their appointed rounds." This quotation was taken from the inscription on front of the Post Office of New York City—from "Herodotus History," 430 B. C., referring to the Persian Post Riders, and from Hoyt's "New Cyclopedia of Practical Quotations," p. 617.)

a growth of cancer with axillary metastases could develop (except perhaps during pregnancy) in a matter of three months. Rather the coexistence of these diseases appears more likely. Reasoning along parallel lines it is somewhat disturbing to note that in Warren's [22] well-documented series, of a total of 42 patients in whom cancer ultimately developed, in 13 of these patients cancer developed during an average follow-up period of only 2.7 years, a relatively brief span considering the natural history of breast cancer.

The second patient withdrawn from the present study was first operated upon at the Johns Hopkins Hospital in 1935, at which time a simple mastectomy was performed for an "intraductal papilloma." In 1951 a recurrence was removed and pathologically considered to be a "low grade papillary carcinoma." Duplicate sections (Figs. 2 *A* and *B*) of the two lesions were submitted to a panel of surgical pathologists, and the consensus was "papillary carcinoma" of both lesions. The "benign" nature of the primary tumor (diagnosed at this hospital) was at variance with the expert consensus, and therefore its validity was challenged and the case was deleted.

RESULTS

Follow-up information revealed that of the 385 patients with benign breast disease who were successfully contacted, there were 271 white women and 114 Negro women. The operative site was right-sided in 192; it was left-sided in 179, and it was bilateral in 14. There appeared to be no significant differences in the several subdivisions of benign breast disease as indicated by the following data:

	White	Negro	Right	Left	Bilateral
Fibroadenoma	178	72	96	95	9
Chronic cystic mastitis	124	29	83	65	5
Papilloma	19	13	13	19	0

The operation of choice was predominantly that of simple excision, which was performed in 92%, or 352 patients. However, in the patients with papilloma, when there was likely to be marked or moderate epithelial hyperplasia, a more extensive operative procedure was often chosen, as indicated by the following data:

	Operation		
	Simple Excision	Simple Mastectomy	Radical Mastectomy
Fibroadenoma	196	4	0
Chronic cystic mastitis	133	17	3
Papilloma	23	6	3

Radical mastectomy performed in six patients was the result of a "suspended sentence" rendered as judgment in the diagnosis of frozen section specimens.

Since 8% of the patients under survey were subjected to mastectomy, it is perhaps proper to assume that the over-all chance for cancer to develop at a later date in these patients with one breast amputated (there were no patients with bilateral amputations) might be slightly less than in a similar group of normal women. However, the not infrequent finding of residual breast tissue within the operative field following mastectomy is unequivocal evidence that such an assumption is not entirely consistent or justified. Indeed, it was the irony of fate that in one patient (in a recent case not included in the present study) breast cancer developed within the scar of a simple mastectomy. Also, benign breast disease is most frequently a diffuse and bilateral process. Thus, it was deemed unnecessary to correct the calculation for so trifling a statistical paradox.

Arranging the ages at operation into quinquennial periods (Table 3), the maximum incidence for fibroadenoma was found to be between the ages of 21 and 25 years; for chronic cystic mastitis, between 41 and 45 years, and for papilloma, between 46 and 50 years. The average age at onset was 30 years for fibroadenoma, 42 years for chronic cystic mastitis, and 47 years for papilloma. This coincides with the observations of most other investigators and clearly indicates the mean age difference of these three types of benign breast disease. In contrast, however, Lane-Claypon (1926) found the average age of women with breast cancer to be 51 years, a striking difference of 21 years between women with fibroadenoma in the present series and women with breast cancer. Although the peak incidence between benign breast disease and breast cancer may be some years apart, as shown in Table 3, there is considerable overlap in the age distribution of both diseases.

Benign breast disease recurred in 50 of 385 patients, thus manifesting a recurrence rate of 13%. It is not plausible to expect that the local excision of a single area of benign breast disease—in a lesion notorious for its diffuse and widespread characteristics—will result in permanent cure. Warren [22] noted a 15% recurrence

TABLE 3.—*Age Distribution*

Benign Breast Disease	Age	< 20	21-25	26-30	31-35	36-40	41-45	46-50	51-55	56-60	61-65	65+	Total Patients
Fibroadenoma	At onset	36	48	33	29	21	18	9	3	2	1	..	200
	At end of follow-up	0	0	17	29	43	29	33	15	20	9	5	200
Chronic cystic	At onset	4	7	9	15	28	39	36	4	5	2	4	153
	At end of follow-up	0	0	3	5	6	16	17	30	33	25	18	153
Papilloma	At onset	0	2	0	5	6	3	7	2	1	3	3	32
	At end of follow-up	0	0	0	0	2	4	5	5	5	3	8	32

rate in patients with "chronic mastitis" and a 17% recurrence rate in patients with "chronic cystic mastitis." When considering this perplexing disease, the diagnostic criteria of which are so often masked by obscure signs and symptoms, it is rather to be anticipated that the opposite breast (composed of identical target organ tissue) will be frequently the site of recurrent benign disease. The surprisingly infrequent recurrence of papilloma in the present series is indicated by the following data:

	Recurrence Benign Breast Disease		
	Same Breast	Opposite Breast	Bilateral
Fibroadenoma	6	8	7
Chronic cystic mastitis	8	11	8
Papilloma	1	1	0
Total	15	20	15

In a total of 7 patients (1.8%) out of 385 breast cancer developed (Table 4). In all seven of these patients subsequent surgery was performed, and the diagnosis of cancer was confirmed by microscopic examination. Although no delay in this condition could be too long, yet the latent period between benign breast disease and cancer varied from 8 to 18 years. A simple surgical excision was the primary operative procedure in all patients. A salient point in the many-sidedness of these statistics is the seemingly inconsistent development of cancer on the side opposite the primary breast disease in four of seven patients. The widespread and bilateral

nature of benign breast disease may best serve to explain the why and wherefore of this finding. The average age of patients with cancer in the present series was 54 years.

A review of all microscopic sections in the seven patients in whom cancer developed revealed cytologic disorganization and epithelial hyperplasia present in five of the primary benign breast lesions. Although the limits of normal may be difficult to determine at times and apparent epithelial hyperplasia may be mistaken for a chance tangential section, yet proliferative epithelial changes with abnormal cellular patterns were noted as relatively frequent findings.

EVALUATION

An appraisal of the foregoing results is predicated upon several major premises. It must be assumed, in the first place, that the removal of a benign breast lesion by simple surgical excision (as occurred in 92% of the patients) did not necessarily eradicate all the abnormal tissue. In a disease in which the borderline between normality and abnormality is at best an indefinite one, it is sheer fantasy to say, as suggested by Atkins,[26] "how many alveoli per square millimetre of cross section

TABLE 4.—*Results of Present Study*

Benign Breast Disease	No. of Patients	Average Age at Onset, Yr.	Average Duration Follow-Up, Yr.	Recurrent Benign Disease		Developed Cancer	
				No.	%	No.	%
Fibroadenoma	200	30	14.1	21	10.5	3	1.5
Chronic cystic mastitis	153	42	13.3	27	17.6	4	2.6
Papilloma	32	47	11.3	2	6.3	0	0.0
Total	385	36	13.6	50	13.0	7	1.8

of breast tissue is to be regarded as normal for any particular age or physiological state of the breast." Underscoring the validity of this assertion is a valuable study by Stout, as reported by Frantz and co-workers.[27] So-called chronic cystic mastitis was found by this eminent surgical pathologist in 74.4% of 1,038 surgical pathologic breast specimens. Some degree of "chronic cystic mastitis" was also noted in other parts of the breast in 78.5% of 410 cases of breast cancer. In a long and comprehensive monograph by Semb,[16] "fibroadenomatosis" was noted in 77% of 122 cases of breast cancer. "Fibroadenomatosis" was diffusely distributed throughout the entire breast tissue in 33% of all cases. In the survey by Foote and Stewart,[18] by using

> . . . the presence of at least one of the cystic or proliferative lesions as a standard for the diagnosis of so-called chronic cystic mastitis, this condition is found in 59 per cent of the 300 cancerous breasts, and in 65 per cent of the 200 noncancerous breasts.

A major contribution to this problem was recently made by Frantz [27] and her colleagues. In a special study of the breasts in 225 routine autopsy cases in which there was no history of previous benign or malignant breast tumors, these investigators found a high incidence of benign breast disease. The ages ranged from 13 to 88 years, and none of the patients were pregnant or lactating at the time of death.

26. Atkins, H. J. B.: Fibroadenosis, Brit. J. Surg. **38**:147-163, 1950.

27. Frantz, V. K.; Pickren, J. W.; Melcher, G. W., and Auchincloss, H.: Incidence of Chronic Cystic Disease in So-Called "Normal Breasts," Cancer **4**:762-783, 1951.

The incidence of chronic cystic disease in these 225 cases of so-called normal breasts was found to be 53%. Gross evidence of cystic disease was actually noted in 19% of the cases and "chronic (proliferative) cystic disease, usually minimal and always bilateral, was found in 28 per cent of the cases." Thus, it appears unlikely that simple surgical excision could possibly eliminate all or even most of the abnormal tissue of benign breast disease.

The second assumption, as suggested by Warren,[22] that must be seriously considered is that the same hormonal imbalances which could conceivably have been responsible for the primary benign breast disease would have the opportunity of continuing to influence the residual breast tissue. The veracity of this proposition is best demonstrated in the present series by the 12% recurrence rate in patients requiring subsequent breast surgery for benign disease. The incidence of recurrence appeared greatest in the opposite breast, yet bilateral recurrences were not at all uncommon. The development of cancer in the opposite breast as often as in the breast requiring primary operation for benign disease adds confirmation to this concept. Recently, we have been distressed by observing one patient who had undergone five separate surgical excisions of fibroadenomata in one breast. The last recurrence was in the scar of her previous simple mastectomy. In this new era of endocrines we have not as yet become beholden to the sex steroids for the prevention of benign breast disease, but "hope is our present day bread."

Lastly, if benign breast disease is to be considered a precancerous condition, then the relative incidence of ultimate breast cancer in the present series should be higher than the incidence of breast cancer in the normal population. The problem of determining this incidence in the normal population for the purpose of comparison is a formidable statistical stint. Warren [22] simply estimates the incidence of breast cancer as being twice the annual death rate. Basing his calculations on a probable over-all cure rate of 20% and an unknown number of patients for whom diagnosis was either not made at all or not recorded on the death certificate, the resultant morbidity can only be regarded as a close but conservative approximation. In the statistical supplement to Geschickter's [28] excellent book, "Diseases of the Breast," the chapter on the relation of chronic cystic mastitis to cancer contains a carefully computed incidence of breast cancer in the normal population by Dr. Louis I. Dublin (Table 5). Despite the complex nature of these calculations the current case rate must not give the misleading impression of rigid mathematical precision. In this analysis, Dublin defines with accuracy and with known uncertainty what would otherwise be more or less inaccurate impressions. However, he is the first to stress "that the results obtained are no more accurate than the assumptions on which they are founded." Although these minor inaccuracies in the statistics of both Warren and Dublin are acknowledged, there is little need for practical concern regarding their trivial probable error.

In accord with the computation method of Warren,[22] the mortality statistics for cancer of the female breast were determined from the "Vital Statistics of the United States for the year 1946" (Table 6). Averaging the breast cancer death rates for the age range 35 to 50 years (chosen specifically because in the present series the average age was 36 years and the average follow-up period was 13.6

28. Geschickter, C. F.: Diseases of the Breast, Philadelphia, J. B. Lippincott Company, 1943.

TABLE 5.—*Chances per 1,000 That a White Woman of a Stated Age Will Acquire a Cancer of the Breast Within the Next Ten Years**

Age, Yr.	Life Table Survivorship Column†	Onset Rate per 100,000	New Cases at Specified Age	New Cases Within Next 10 Yr.	Chances per 1,000 of Acquiring a Cancer of the Breast Within Next 10 Yr.
35	88,608	16.6	14.7	244.5	2.8
36	88,272	18.8	16.5		
37	87,922	21.2	18.6		
38	87,557	23.8	20.8		
39	87,178	26.4	23.0		
40	86,785	29.2	25.3		
41	86,377	32.1	27.7		
42	85,951	35.1	30.2		
43	85,505	38.1	32.6		
44	85,035	41.3	35.1		
45	84,538	44.5	37.6	461.8	5.5
46	84,010	47.6	39.9		
47	83,447	50.6	42.2		
48	82,847	53.2	44.1		
49	82,208	55.7	45.8		
50	81,527	58.1	47.4		
51	80,803	60.2	48.6		
52	80,034	63.2	50.5		
53	79,219	65.7	52.0		
54	78,357	68.5	53.7		
55	77,445	71.3	55.2	581.9	7.5
56	76,478	74.0	56.5		
57	75,447	76.3	57.5		
58	74,343	78.6	58.4		
59	73,154	80.7	59.0		
60	71,871	82.6	59.4		
61	70,483	84.4	59.5		
62	68,983	86.1	59.4		
63	67,365	87.5	58.9		
64	65,623	88.6	58.1		
65	63,755	89.7	57.2	513.2	8.1
66	61,763	90.8	56.1		
67	59,649	92.7	55.3		
68	57,421	94.0	54.0		
69	55,085	96.1	52.9		
70	52,644	98.3	51.7		
71	50,098	100.2	50.2		
72	47,444	101.1	48.0		
73	44,678	101.4	45.3		
74	41,800	101.7	42.5		

* Calculations were made by Dr. Louis I. Dublin, and used with permission of Dr. Charles F. Geschickter, author, and J. B. Lippincott Company, publishers, of "Diseases of the Breast," Ed. 2, 1945, Table 36, p. 286.
† Number of survivors to specified age out of 100,000 born alive, according to life table for white women in the United States, 1936.

TABLE 6.—*Cancer of the Female Breast, Deaths and Death Rates by Age** *(United States, 1946)*

Age, Yr.	No. of Deaths	% of All Female Cancer Deaths	Death Rate†
All ages	17,274	18.5	24.4
35-39	759	24.1	14.5
40-44	1,208	24.9	25.1
45-49	1,712	23.8	39.4
Average of ages 35-49	1,226	24.3	26.3

* These data were taken from "Vital Statistics of the United States, 1946," United States Bureau of Census, Population, Special Reports, Series P-47, No. 3.
† Rates are the number of deaths in a specified group per 100,000 estimated midyear population of that group.

years), the caculated annual mortality rate was found to be 0.052 per 100. Thus, during an average period of 13.6 years of follow-up survey the expected incidence of breast cancer in the present series should have been 0.70%. The actual incidence, as indicated in Table 4, was 1.8%, or 2.6 times the expected rate, as determined according to the assumptions of Warren.

In accord with the predetermined caculations of Dublin (Table 5) the chances of acquiring a cancer of the breast within the average follow-up period of 13.6 years should be simply the sum total for this period of years of the onset rates per 100,000 population. Since the average age at onset of benign breast disease in the present series was 36 years, the computation in Table 5 should begin at age 36 and continue by the summation of onset rates for the succeeding 13.6 years. Thus, the chances of acquiring breast cancer within the average follow-up period of 13.6 years should have been 0.50%. The actual incidence, as indicated in Table 4, was 1.8%, or 3.6 times the expected rate, as determined by the assumptions of Dublin.

In comparing the breast cancer rate in the present series with parallel recent studies of Warren,[22] in Boston, and Clagett,[29] at the Mayo Clinic, there is indeed a striking similarity of results. The breast cancer rate for females with preexisting benign breast disease was 4.5 times as great as expected for all women in the normal population in Warren's series, 5 times as great in Clagett's series, and 2.6 to 3.6 times as great in the present series. In marked contrast with Warren's data, however, there was no predominance of breast cancer noted in our patients below the age of 50 years.

In fortifying our findings against the prejudice of possible error it is well to note that at least one weak point in the present study rests with the number of patients "lost" to follow-up. There were 66 patients or 15% of the total number who could not be accurately traced. It might be supposed that some of those patients have been "lost" because of death—a few perhaps dying of breast cancer some years ago beyond the range of recent memory. This could give the illusion of even a higher incidence of breast cancer following benign breast disease. Such a speculation, however, is pure surmise and invites nothing but suspicion.

Although a significant difference in the peak incidence of the three types of benign breast disease (Table 3) was noted in the present series, yet considerable overlap in the age distribution occurred, with at least 81 patients past 45 years of age at the onset of their benign disease. However, the over-all average age at onset was only 36 years and the follow-up period, though considerable in range and longer than in any similar study, averaged 13.6 years. Thus, if the average patient was followed for the average period of time, she would not have reached the average age of onset (51 years) for breast cancer. Despite the problems and practical limits of a long-term follow-up survey, it would have been even more gratifying if a larger number of patients had been followed over a longer period of time.

Finally, one must consider the significance of operative trauma to the breast incident to the primary surgical excision as a possible cause of cancer. It is sound contemporary opinion that if local operation with its consequent rupture of the ductacinar system was closely allied to the origin of breast cancer, one might expect to find frequent evidence of injury and scarring associated with breast cancer. Also

29. Clagett, O. T.; Plimpton, N. C., and Root, G. T.: Lesions of the Breast: The Relationship of Benign Lesions to Carcinoma, Surgery **15**:413-419, 1944.

trauma, as is well known, is more likely to cause sarcomatous changes than carcinomatous. Yet neither of these occurred with any degree of frequency. However, cancer as a sequel to chronic injury and war wounds has been reported (Gillis and Lee, 1951) [30] in which neoplastic changes were noted more than 30 years after World War I. The very fact that in only three of seven patients in the present series did cancer develop in the same breast previously operated upon undermines the support of this contention.

COMMENT

The earliest studies of the relationship between benign breast disease and cancer were primarily descriptive and speculative. More modern investigation is based upon evidence that is experimental, histological, and clinical or statistical.

Experimental.—Breast cancer can be produced in mice and rats by intensive and prolonged estrogenic administration. The pioneer studies of Goormaghtigh and Amerlinck [31] discovered the cystic changes which occur in the castrate female mouse breast after prolonged estrogen (follicular) stimulation. The development of cancer occurred in 1 out of 11 mice of an impure stock. These authors concluded that the parallelism between the lesions of benign breast disease in the human and in the mouse was *quasi complet*. The classic work of Lacassagne [32] indicated that changes characteristic of benign breast disease are often a precursor to breast cancer produced in response to estrogenic stimulation of mice. Geschickter [28] has demonstrated that various initial changes, such as cyst formation and the development of fibroadenoma, may also occur in the rat in response to prolonged and intensive estrogenic stimulation. Although these changes characteristic of benign breast disease are not necessarily essential to the subsequent development of breast cancer, when they do occur they are in response to the administration of estrogens. The cystic and proliferative changes produced in rats by Eisen [33] with cystalline estrogen correspond to similar lesions in the human female.

Pullinger [34] points out that Lett,[35] in 1905, speculating on the relation between ovarian secretion and chronic mastitis wrote:

> Carcinoma, as is well known, not infrequently develops in a breast which is already the seat of a chronic mastitis, and it may be that there is a connexion between the secretion of the ovary, one or more of the varieties of chronic mastitis, and mammary cancer.

In a distinguished group of carefully conducted experiments, Pullinger [34] demonstrated that estrogen alone could produce adenosis with duct-acinar distention and

30. Gillis, L., and Lee, S.: Cancer as a Sequel to War Wounds, J. Bone & Joint Surg. **33-B**:167-179, 1951.

31. Goormaghtigh, N., and Amerlinck, A.: Réalisation expérimentale de la maladie de Reclus de la mamelle chez la souris, Bull. Assoc. franç. étude cancer **19**:527-543, 1930.

32. Lacassagne, A.: Apparition de cancers de la mamelle chez la souris mâle, sourmise à dez injections de folliculine, Compt. rend. Acad. sc. **195**:630-632, 1932.

33. Eisen, M. J.: Occurrence of Benign and Malignant Mammary Lesions in Rats Treated with Crystalline Estrogen, Cancer Res. **2**:632-644, 1942.

34. Pullinger, B. D.: Cystic Disease of the Breast: Human and Experimental, Lancet **2**:567-572, 1947.

35. Lett, H.: An Analysis of 99 Cases of Inoperable Carcinoma of the Breast Treated by Oöphorectomy, Med.-Chir. Tr. **88**:147-189, 1905.

secretion without the combined action of progesterone or prolactin. These changes in mice were independent of the milk factor, or failure of involution, or of breast cancer. It is the opinion of Pullinger

> . . . that the capacity to react by cystic dilatation combined with adenosis-like proliferation, which is hereditary in certain strains (of mice), is not correlated with the hereditary factor which underlies susceptibility to cancer.

In certain respects this idea substantiates the belief of Cheatle and Cutler [19] that benign breast disease in humans begins as an independent entity, quite apart at the start from cancer, yet a chain of events may ultimately lead to the transition of hyperplasia to neoplasia. In studying the problem of where and how the steroid hormones interfere with dynamics of cancer, Lipschutz,[36] working with guinea pigs, found that adenocarcinoma of the breast never developed despite prolonged administration of estrogens. Fibroadenomas of the breast occasionally occurred, but these tumors were much less striking than the estrogen-induced fibroids within the abdominal cavity.

Much of the preceding experimental essay has one serious defect; all conclusions are based upon experimental research with rodents. Although Pullinger [34] considers human and experimental cystic disease comparable and brought about by an excess of estrogens, yet the decisive factor in each case is the atypical response of the target tissue. Perhaps, as suggested by Foote and Stewart,[18] "the physiologic gap between the two species is too wide for mutual transposition of morphologic observations." However, the failure to produce experimental breast disease or tumors in a primate, the Macacus rhesus monkey, after years of continuous estrogen administration adds to one's scepticism in transposing results from one species to another.

Although the critical role of the steroid hormones has been sufficiently demonstrated in the pathogenesis of breast cancer in rodents, yet a systematic study by members [37] of the Committee on Research of the American Medical Association, concerning the effects of massive and prolonged estrogen therapy in patients with advanced or metastatic breast cancer has revealed neither the induction of benign breast disease or of secondary breast cancer in these postmenopausal women. Even after several years of intensive therapy with estrogens and/or progesterone, biopsy specimens of breast tissue in these postmenopausal patients reveal few histologic changes characteristic of benign breast disease. However, the development of gynecomastia, with proliferation of all breast elements, which occurs after prolonged estrogen administration for prostatic cancer, is highly suggestive of specific target organ tissue growth. The untoward development of breast cancer in the male as a result of exogenous estrogens is fortunately infrequent, but this local manifestation of an upset hormone balance is a conversion of considerable importance. Having only this much data to go on, it remains impossible at present to precisely relate the pathologic picture of benign breast disease to an estrogenic steroid surfeit.

Histologic.—The best proof of the causal relationship between benign breast disease and cancer would be the simple and direct histologic demonstration that

36. Lipschutz, A.: Steroid Hormones and Tumors, Baltimore, Williams & Wilkins Company, 1950.

37. Lewison, E. F., and Chambers, R. G.: The Sex Hormones in Advanced Breast Cancer, New England J. Med., to be published.

the point of departure in breast cancer begins in a nidus of benign breast disease. Although Foote and Stewart [18] are at a loss for precise figures, "we can confidently say that we have seen cancer begin in duct papillomatosis, solitary and multiple, cyst, apocrine and epithelium and blunt duct adenosis."

Campbell [17] has carefully reviewed the literature and found many exponents of the "evolutionary" theory of benign breast disease in which simple cystic processes gradually assume more and more hyperplastic forms, passing imperceptibly from benign to malignant breast tumors. Cheatle and Cutler [19] describe "desquamative epithelial hyperplasia," wherein cysts are formed which may pass gradually from benign to malignant hyperplasia or neoplasia. Ewing [38] found precancerous changes in a number of breasts removed for benign disease. Increasing epithelial overgrowth was considered the forerunner of breast cancer in at least some cases originating in an area of cystic disease.

Among some surgical pathologists there seems to be a sort of clairvoyant conviction in the evolution of epithelial hyperplasia to neoplasia. There can be no contradiction, no diversity of opinion concerning the precancerous potential of benign breast disease. All of us, perhaps, are similarly blameworthy in believing most that which we understand least. However, Atkins [26] is more circumspect about the charm of these histologic inventions and inspirations:

> Histologically the game of arranging a number of microscopic slides in a series showing a normal breast at one end of the scale, all the intermediate phases of fibroadenosis in the middle, and cancer at the other, is one which few histologists can resist playing.

Yet the sequence of such evidence merits most serious consideration and the ridicule of *reductio ad absurdum* by showing "that the normal breast develops from carcinoma through all stages of fibroadenosis in the reverse order" is hardly a test of truth. In the opinion of Atkins, one of the most important "fallacies in the histologic argument" is that it fails to "take into account the striking fibrous-tissue reaction which accompanies the epithelial changes, and which has no part in the stimulation of cancer and may indeed be inimical to it." It is possible, however, that this superfluous fibrous-tissue response may be but a "monument of mutability" in the body's effort to safeguard itself against the ravages of an unknown and invisible pathogenic force. Such a teleological concept is unacceptable to Atkins [26] because it is "incapable of either proof or disproof."

Campbell [17] has summed up the histologic evidence presented in favor of the precancerous theory of benign breast disease:

> 1. Cystic disease is frequently found in association with frank carcinoma.
>
> 2. Various gradations of epithelial proliferation may exist to give the impression that cystic disease represents a progressive evolution of epithelial hyperplasia eventuating in carcinoma.

Clinical.—Having thus been thwarted by the many millstones around microscopic evidence, as well as by the limits of information contigent upon present experimental methods, perhaps the most practical and direct approach to the problem is the clincal follow-up technique. Does cancer follow benign breast disease in a higher proportion of patients than in the normal population? What is the clinical behavior of a benign breast lesion over the course of years and how does its histologic appearance conform to follow-up results?

38. Ewing, J.: Neoplastic Diseases, Ed. 3, Philadelphia, W. B. Saunders Company, 1928.

Statistics, it is said, are no substitute for clinical judgment. Yet in the absence of reliable diagnostic criteria for benign breast disease (Atkins [26] believes "that clinically there is no beginning point" for fibroadenosis), our ignorance must not serve as a wetnurse to complacency. Seasoned statistics are the scaffold of experience upon which is built sound clinical judgment. At present the most reliable method of determining the relationship between cancer and benign breast disease is the long term follow-up of a substantial group of patients.

Over the course of years there have appeared many and varied reports (Table 1) on the tendency of cancer to follow benign breast disease. In some of these reports the nature of the study is responsible for the character of the lame and confusing conclusions. A large number of patients were "lost" to follow-up. The early age at onset or the trifling time of follow-up may have made the results unworthy of serious consideration. The validity of the diagnosis, clinical or pathologic, was often found wanting or scarcely substantiated by the evaluation of so controversial a subject. Nevertheless, there is sufficient competent evidence to indicate that a positive relationship exists between benign breast disease and cancer. However, there are certainly no decisive studies favoring one specific type of benign breast lesion over another as being particularly precancerous. Resignation to this fact may be disappointing, but there is no alternative.

In a unique follow-up study performed by putting the cart before the horse, Foote and Stewart [18] reviewed the records of 1,200 patients with operable breast cancer and found a previous history of benign breast disease (confirmed by operation) in 2.4%. For control purposes the records of 1,200 patients with cancer elsewhere in the body were reviewed. Of these 1,200 patients with nonbreast cancer, only 1.08% had a previous history of benign breast disease (confirmed by operation). It is of particular interest to note in their discerning commentary that only a 10-year follow-up period would have been insufficient to show the development of 7 out of 12 cases of breast cancer. An average follow-up period of 13.6 years may perhaps haunt our present study with a similar suspicion, but the maximum span of 25 years, with 75% of the patients followed longer than 10 years (Tables 7 and 8), makes this possibility less likely. Yet in six out of seven cases in the present series, cancer following benign breast disease occurred after an interval of nine years.

The results of this study reveal that women with benign breast disease show a limited but distinct predisposition to the development of cancer when compared with normal women in a similar age range. Although Warren [22] points out that the danger of breast cancer developing is particularly marked in women prior to the menopause, we have not found this to be true. In the present series the average age of patients at cancer onset was 54 years, with all women in the menopause period or beyond. Despite the increased incidence of breast cancer in the older age groups (Table 5) these postmenopausal women must by definition alone be past the peak of their endocrine prime. Thus, if benign breast disease is associated with abnormal hormonal stimulation, then the danger of cancer as its sequel must be associated with a long latent period. This is indeed quite characteristic of certain occupational cancers.

It seems a safe and salutary scheme to suggest that all patients with benign breast disease be examined at periodic intervals. The efforts of the American Cancer Society toward educating all women in the value and technique of self-

examination are particularly praiseworthy. Regardless of the individual interpretation of existing evidence, there appears to be a basic relationship between benign breast disease and cancer. Present knowledge indicates a small but firm core of common agreement on this subject, surrounded by a wide variety of individual differences of opinion. Certainly, the experimental evidence is strongly suggestive, the histologic study is apparently indicative, and the clinical statistics are perhaps the most impressive, although the precise importance of benign breast disease as a pre-

TABLE 7.—*Period of Follow-Up*

Benign Breast Disease	5 Yr. or Less	6-10 Yr.	11-15 Yr.	16-20 Yr.	21-25 Yr.	Total Patients	Average Follow-Up, Yr.
Fibroadenoma	4	43	88	48	17	200	14+
Chronic cystic mastitis	5	30	76	30	12	153	13+
Papilloma	4	11	11	5	1	32	11+
Total patients	13	84	175	83	30	385	13.6

TABLE 8.—*Duration of Follow-Up by Age Decades*

Age at Onset, Yr.	Average Duration of Follow-Up, Yr.
<29	14.1
30-39	13.6
40-49	14.0
50-59	12.5
60+	11.5

TABLE 9.—*Summary of Data on Seven Patients in Whom Breast Cancer Developed*

	No.	Primary Operation	Side of Primary Operation	Age at Onset, Yr.	Age Cancer Developed, Yr.	Interval Benign Disease to Cancer, Yr.	Side Cancer Developed
Fibroadenoma	1	Simple excision	Right	29	47	18	Left
	2	Simple excision	Left	54	62	8	Left
	3	Simple excision	Right	31	49	18	Right
Chronic cystic	4	Simple excision	Right	42	51	9	Left
mastitis	5	Simple excision	Right	45	55	10	Left
	6	Simple excision	Right	40	51	11	Left
	7	Simple excision	Bilateral	38	48	10	Left
Papilloma	None						

cursor of breast cancer depends upon the still unpenetrated cause of these diseases. Yesterday's yardsticks for the detection and diagnosis of breast pathology may have been too yielding. Perhaps future wisdom will forgive our present clumsiness and in the full light of tomorrow we shall be able to look forward toward the conquest of both benign and malignant breast disease. Until then, however, the teachings of Sir Astley Cooper (1829) [8] still serve as our surest safeguard and the source of inspiration for our own modest efforts:

> Though no specific remedy may yet have been discovered for the cure of some diseases, it is still a great advantage to be able to discriminate curable from incurable cases; the dangerous from the slight; those which require surgical operations from those which do not demand them; and such as admit of a trifling operation from those which call for one of extreme severity.

SUMMARY

The present study constitutes a long-term follow-up survey of all patients with benign breast disease operated upon at the Johns Hopkins Hospital during the period 1925 to 1942. During this time a total of 451 patients were operated upon, of whom 85.4%, or 385 patients, were successfully followed over a 1- to 25-year survival span.

The average follow-up period was 13.6 years, with 75% of the patients being followed from 10 to 25 years.

The pathologic diagnosis was fibroadenoma in 200 patients, chronic cystic mastitis in 153 patients, and papilloma in 32 patients.

According to age, the maximum incidence of fibroadenoma was found in patients between 26 and 30 years of age, of chronic cystic mastitis in patients between the ages of 41 and 45, and of papilloma in patients between the ages 46 and 50. The over-all average age at onset of benign breast disease was 36 years.

The primary operation was predominantly that of simple excision, which was performed in 92%, or 352 patients. Benign breast disease recurred in 50 (13%) of 385 patients.

Cancer of the breast developed in 7 (1.8%) of the 385 patients surveyed.

When compared with the "normal" incidence of breast cancer in females of a similar age group, the chances of acquiring breast cancer appeared to be 2.6 to 3.6 times as great in the present series as in the general female population. The variation in results was determined by different methods of statistical analysis.

The experimental, histological, and clinical or statistical evidence bearing upon the relationship between benign breast disease and cancer is reviewed and discussed. Although a correlation between the two appears evident, there is no indication in the present study that one type of benign breast disease is any more precancerous than another.

CONCLUSIONS

The present study is in accord with current knowledge which indicates a small but firm core of common agreement regarding the predisposition of patients with benign breast disease to breast cancer. Thus, it is a salutary safeguard to suggest that all patients with benign breast disease be regularly examined at periodic intervals.

Hartford Hospital, Hartford, Conn. (Dr. Lyons).

MIDTHIGH AMPUTATIONS FOR ARTERIOSCLEROTIC AND DIABETIC GANGRENE

Analysis of One Hundred Thirteen Consecutive Amputations in One Hundred Eight Patients, 1939 to 1952

LOUIS CARP, M.D.
NEW YORK

MIDTHIGH amputations for gangrene resulting from peripheral vascular disease, arteriosclerotic and/or diabetic, have presented a number of important problems which have a direct relationship to morbidity and mortality. They include procrastination and timing of operation; technical methods; closed versus open stumps; anesthesia, especially the contraindicated refrigeration anesthesia with tourniquet; postoperative stump care, and supportive and nutritional therapy.

During World War II, the Surgeon General's Office deemed it advisable to adopt a standard method for midthigh amputations, leaving the stumps open and applying traction. This was sound practice in comparatively young men, whose wounds almost always had virulent mixed infections and frequent long latent periods before operative therapy. It was also possible that this procedure was safer in the hands of those with limited experience. Medical officers became so thoroughly indoctrinated with the principle of traction on stumps which were left open that some of them have permitted this method to become standard in amputations for peripheral vascular disease in civilian practice. This management predominated as a routine in a group of our cases immediately after the war. It has been our experience that such management is appropriate and advantageous in those selected cases in which there is obvious ascending infection or thrombosis of the femoral vessels. However, it has also been our experience, as well as that of others [1] before and during the antibiotic period, that midthigh amputations for peripheral vascular disease, arteriosclerotic and/or diabetic, can be effectively handled by tight or loose closure, depending on the clinical condition and on the extent of blood vessel involvement which is ascertained during operation. Our statistics (Table 6) and the precautionary operative techniques and postoperative care will demonstrate the advisability of this practice, so that the stumps heal satisfactorily and comparatively quickly. When the open stump technique is used, wounds take much longer to heal; asepsis and nitrogen and electrolyte balance are difficult to maintain; secondary hemorrhage is more possible, and an end-bearing stump is produced, which may be far from satisfactory and frequently in need of revision.

From the Second Surgical Division, Goldwater Memorial Hospital.

Read before the Fifth Annual Meeting, the Gerontological Society, Washington, D. C., Sept. 5-7, 1952.

1. (*a*) Mandelberg, A., and Sheinfeld, W.: Diabetic Amputations: Amputation of Lower Extremity in Diabetics; Analysis of 128 Cases, Am. J. Surg. **71**:70-76 (Jan.) 1946. (*b*) Kern, H. M.: Amputation of Lower Extremities in the Aged, ibid. **82**:479-484 (Oct.) 1951.

STATISTICAL ANALYSIS

Our clinical material represents 113 consecutive midthigh amputations in 108 patients between the years 1939 and 1952 in a large municipal hospital for prolonged illnesses. The patients were chiefly bad risks in the older age groups. They were chronically ill from degenerative disease, which was often accompanied by malnutrition and psychiatric disorders. Delay in operation by procrastination, either through well-intentioned conservatism or late consent for operation, contributed not only to rapid deterioration of the patient and to diminished resistance and homeostasis, but to the added chances of swift ascending infection, thrombosis, and poor stump healing. Kern,[1b] Cutler,[2] and Holden [3] have shown that in most cases attempted conservatism by preliminary toe amputations has not been success-

TABLE 1.—*Description of Population, 1939 to 1952*

Total Patients		Arteriosclerotic				Diabetic			
		Men		Women		Men		Women	
No.	Age, Yr.	1939-1945	1946-1952	1939-1945	1946-1952	1939-1945	1946-1952	1939-1945	1946-1952
4	Under 60	1	1	..	..	..	1	1	..
42	60-69	15	6	..	2	4	2	3	10
48	70-79	8	11	4	5	4	5	4	7
13	80-89	4	4	..	1	1	1	..	2
1	90-99	..	..	..	1	..	..	..	..
108		28	22	4	9	9	9	8	19

TABLE 2.—*Anesthesia**

Agent	Patients, No.	1939-1945	Deaths, No.	1946-1952	Deaths, No.	Total Deaths
Cyclopropane	40	15	5	25	7	12
Refrigeration with tourniquet	40	26	12	14	9	21
Thiopental sodium	16	..	..	16	5	5
Spinal	10	10	2	..	..	2
Nitrous oxide	1	1	1	..	..	1
Nitrous oxide and ether	3	1	..	2	2	2
Ether	3	..	..	3	2	2
Total	113	53	20	60	25	45

* Five patients had bilateral amputations.

ful, especially in the presence of moist gangrene, and that valuable time was lost and the risk increased before the eventual midthigh amputation was carried out. Standard methods of supportive treatment have been used in all cases. Up to 1946, chemotherapy was available. After that, both chemotherapy and, chiefly, antibiotic therapy have been valuable therapeutic agents before and after operation.

Statistical analysis is difficult because of many variable factors, including the general condition of the patient and the degree of severity of the surgical pathological changes. In some cases specific information was not noted in the hospital record. However, the over-all picture has led to the formulation of some basic principles, indications, and contraindications.

2. Cutler, C. W., Jr.: Urgent Surgery in the Aged, Ann. Surg. **126**:763-779 (Nov.) 1947.

3. Holden, W. D.: Arteriosclerotic Ischemic Necrosis of Lower Extremities, Surgery **22**:125-128 (July) 1947.

TABLE 3.—*Related Causes of Death**

	No. of Autopsies	1939-1945	1946-1952	No. of Cases
Pulmonary parenchymal	6	6	4	10
Cardiac failure	2	6	3	9
Thrombosis and embolism	4	..	4	4
Coronary thrombosis	..	..	1	1
Cerebral thrombosis	..	1	1	2
Gangrenous stump, B. welchii	2	1	1	2
Hemorrhage				
Peptic ulcer	1	1	..	1
Rectal	..	1	..	1
Femoral artery	1	..	1	1
Shock	1	1	2	3
Heat exhaustion	..	..	2	2
Decubitus ulcers	..	..	2	2
Sepsis	..	1	1	2
Unknown	..	2	3	5
Total	17	20	25	45

* The average survival time for 45 patients was 23 days.

TABLE 4.—*Principal Autopsy Causes of Death in Eleven Cases of Arteriosclerotic Gangrene with Refrigeration Anesthesia and Tourniquet* *

		No. of Cases
Thrombosis		5
Pulmonary artery	2	
Abdominal aorta	1	
Superior mesenteric artery	1	
Femoral artery	1	
Embolism of pulmonary artery		1
Cardiac failure		3
Bronchopneumonia		1
Arteriosclerotic ulcer		1
Stomach with hemorrhage		..
Total		11

* Three deaths from thrombosis occurred in the third surgical division, and these are not discussed in this paper. There were no cases of thrombosis as causes of death seen at autopsy on patients with diabetic gangrene.

TABLE 5.—*Effect of Refrigeration Anesthesia with Tourniquet on Stump Healing, Breakdown, and Mortality*

	Healed	Stump Breakdown	Died	Cases, No.
Cases Observed 1939-1945				
Arteriosclerotic				
Suture closure	4	7*	8	14
Open with traction	..	..	..	..
Diabetic				
Suture closure	8	..	4	12
Open with traction	..	..	..	..
Total	12	7	12	26
Cases Observed 1946-1952				
Arteriosclerotic				
Suture closure	..	..	1	1
Open with traction	4	..	4	6
Diabetic				
Suture closure	2	..	..	2
Open with traction	1	..	4	5
Total	7	..	9	14
Grand total	19	7	21	40

* Five of these seven patients subsequently died.

TABLE 6.—*Operative Analysis and Results in One Hundred Thirteen Midthigh Amputations in One Hundred Eight Patients, 1939 to 1952*

Total Cases	Total Deaths	Method of Closure	No. Cases		Average Healing Time				Revision of Stump		No. Deaths		Related Causes of Death			
					1939-1945		1946-1952						1939-1945		1946-1952	
			1939-1945	1946-1952	Days	Cases	Days	Cases	1939-1945	1946-1952	1939-1945	1946-1952	Autopsy	Clinical	Autopsy	Clinical
													Arteriosclerotic Group			
12	5	Skin	11	1	30	7	..	..	1	..	4	1	(1) Lobar pneumonia pulmonary abscess, 1 day; (2) bleeding gastric ulcer, 10 days	(1) Cardiac failure, 3 days; (2) cardiac failure, 23 days	.....	(1) Decubitus ulcers, 22 days
..	..	Muscle	..	..	..	..	..	..	..	..	..	..	.....	.....	.....	.....
..	..	Fascia	..	..	..	..	..	..	..	..	..	..	.....	.....	.....	.....
1	..	Muscle and fascia	1	..	?	?	..	..	..	..	..	..	.....	.....	.....	.....
6	2	Muscle and skin	6	..	35	?	..	..	2	..	2	..	(1) Gangrenous stump, cardiac failure, gangrenous cystitis, 2 days	(1) B. welchii sepsis, 40 days	.....	.....
12	6	Fascia and skin	10	2	29	8	7	1	..	..	5	1	(1) Cardiac failure, 1 day; (2) bronchopneumonia, pericarditis, 23 days	(1) Pneumonia, 14 days; (2) shock, 2 days; (3) unknown, 20 days	(1) Pulmonary artery thrombosis, 19 days	.....
19	9	Muscle, fascia, skin	7	12	23	6	10	5	1	..	2	7	.....	(1) Cardiac failure, 85 days; (2) cardiac failure, 18 days	(1) Pulmonary embolus, 2 days	(1) Cardiac failure, 3 days; (2) sepsis, 18 days; (3) heat exhaustion, 2 days; (4) shock, 7 days; (5) bronchopneumonia, 26 days; (6) unknown, 20 days
15	7	Open with traction	..	15	..	..	57	6	..	..	..	7	.....	.....	(1) Pulmonary edema, 2 days; (2) saddle embolus, contralateral gangrene, 2 days; (3) saddle embolus, contralateral gangrene, 3 days; (4) cardiac failure, 22 days; (5) pulmonary edema, 3 days	(1) Heat exhaustion, 2 days; (2) cause unknown, 50 days
Total																
65	29		35	30	..	..	..	..	4	..	13	16	5	8	7	9

													Diabetic Group			
3	2	Skin	3	..	10	1	..	..	..	..	2	..	.....	(1) Pulmonary edema, 10 days; (2) rectal hemorrhage, 8 days	.....	.....
..	..	Muscle	..	..	..	..	..	..	..	..	..	..	.....	.....	.....	.....
..	..	Fascia	..	..	..	..	..	..	..	..	..	..	.....	.....	.....	.....
1	1	Muscle and fascia	..	1	..	..	..	..	..	..	..	1	.....	.....	(1) Shock (death on table)	.....
8	2	Muscle and skin	8	..	46	5	..	..	1	..	2	..	(1) Pulmonary tuberculosis, bronchopneumonia, cardiac mural thrombi, 15 days	(1) Cerebral accident, 7 days	.....	.....
6	1	Fascia and skin	2	4	10	2	10	4	..	..	1	..	.....	(1) Cardiac failure, 21 days	.....	.....
15	2	Muscle, fascia, skin	5	10	25	4	..	..	..	..	2	..	.....	(1) Pulmonary edema, sepsis, 1 day; (2) cause unknown, 50 days	.....	.....
15	8	Open with traction	..	15	..	..	51	8	..	..	..	8	.....	.....	(1) Hemorrhage femoral artery, 75 days; (2) pulmonary edema, 24 days; (3) gas gangrene, gangrenous stump, decubitus ulcers, 37 days	(1) Decubitus ulcers, 60 days; (2) coronary thrombosis, 25 days; (3) cerebral thrombosis, contralateral gangrene, 33 days; (4) cardiac failure, 7 days; (5) unknown, 42 days
Total																
48	16		18	30	..	..	..	..	1	..	7	9	1	6	4	5
Grand Total																
113	45		53	60	..	..	..	..	5	..	20	25	6	14	11	14

Description of Population (Table 1).—There was a total of 108 patients, 5 of whom had bilateral amputations. Sixty-eight were men and 40 women. The youngest patient was 51 years of age and the oldest 94. Forty-eight were in the eighth decade, 42 in the seventh, and 13 in the ninth. The men predominated in the arteriosclerotic group (50 out of 63) and the women in the diabetic group (27 out of 45).

Anesthesia (Table 2).—A total of 113 anesthesias were carried out, with 45 deaths. Between 1939 and 1952 there were 40 patients who had refrigeration anesthesia with tourniquet, of whom 21 died. Over the same period there were 40 patients who had cyclopropane anesthesia, of whom 12 died. A comparison between the number of deaths among patients who had refrigeration anesthesia (21 deaths out of 40) and the remaining patients who had other types of anesthesia (24 out of 73) points to the greater hazard of refrigeration anesthesia.

Related Causes of Death (Table 3).—The principal causes of death among 45 patients, on 17 of whom autopsies were performed, were bronchopneumonia, cardiac failure, and thrombosis and embolism. At the Goldwater Memorial Hospital between 1939 and 1952, 11 autopsies are recorded (Table 4) of patients who had midthigh amputations for arteriosclerotic gangrene under refrigeration anesthesia with tourniquet. Six of these patients died of massive thrombosis in major blood vessels or of embolism.

It is significant that three patients died of hemorrhage, one from the femoral artery in a stump which was left open with traction, another from a peptic ulcer, and the third from an unknown lesion in the colon or rectosigmoid. Three patients died of shock, one on the operating table and two of heat exhaustion. The average survival time was 23 days.

Refrigeration Anesthesia with Tourniquet: Stump Healing, Stump Breakdown, and Mortality (Table 5).—Of a total of 40 patients given this method of anesthesia, healing occurred in 19 and 21 died. Five of the latter had stump breakdowns, but there were two other patients with stump breakdowns who lived. All these 7 patients had stump closure during the period 1939 to 1945. It is presumed that the major causative factor was the anoxia of the tissues from prolonged tourniquet application of from two to four hours. During the antibiotic period, 13 patients had open stumps with traction. One of these stumps broke down, and nine of the patients subsequently died.

By comparison, there were also 40 patients operated upon under cyclopropane anesthesia, with 12 deaths (Table 2). Thirty-five stumps were closed, of which three broke down (Table 7). This might not have occurred if the stumps had been inspected earlier and appropriate measures taken for drainage. Five stumps were left open with traction, of which one broke down. The patient died of Clostridium perfringens (Bacillus welchii) sepsis.

It therefore becomes apparent that the greater number of breakdowns in the refrigeration anesthesia group can be attributed to the prolonged tissue anoxia from the tourniquet and possibly also from thrombosis of the smaller vessels.

Healing Time: Closed Versus Open Stumps (Table 6).—Any attempt to appraise the healing time of stumps is difficult because the hospital records were deficient in adequate notations in many cases. There are, however, some significant observations from the data at hand. The healing time for arteriosclerotic and diabetic patients was practically the same. Between the years 1939 and 1945, the

average healing time in 39 of the closed cases was 27 days, whereas between 1946 and 1952 it was 10 days in 10 cases. This reduced time may be attributed to the use of antibiotics and to better technique and supportive therapy. There were no open cases with traction between the years 1939 and 1945, but from 1946 to 1952 there were 14 such cases in which notations on healing time were made, and the average time was 54 days. One of these patients died of a gangrenous stump, with Cl. perfringens sepsis. At present, therefore, it takes approximately five times as long for an open stump to heal as for a closed stump. The total mortality rate among patients who had open stumps with traction was 50%. By comparison, it was 37% in those who had closed stumps. Table 7 shows that there was a total of 14 stump breakdowns among all the amputations. Eleven of them occurred in closed stumps during the period 1939 to 1945, of which seven followed refrigeration anesthesia with tourniquet. One open stump broke down during 1946 to 1952. Thiopental (pentothal®) sodium was used as an anesthetic. Considering all the factors, closed stumps are preferable in properly selected cases.

TABLE 7.—*Analysis of Stump Breakdowns*

	Amputations			Breakdowns, No.								
				Closed Stump				Open Stump				
				1939-1945		1946-1952		1939-1945		1946-1952		Total Breakdowns
Anesthesia	Total	Closed No.	Open No.	Arterio-sclerotic	Diabetic	Arterio-sclerotic	Diabetic	Arterio-sclerotic	Diabetic	Arterio-sclerotic	Diabetic	
Cyclopropane	40	35	5	..	1	1	1	..	..	..	..	3
Refrigeration with tourniquet	40	28	12	7	..	..	..	..	..	..	..	7
Thiopental sodium	16	5	11	..	..	..	..	..	..	..	1	1
Spinal	10	10	..	3	..	..	..	..	..	..	..	3
Nitrous oxide	1	1	..	..	..	..	..	..	..	..	..	..
Nitrous oxide and ether	3	2	1	..	..	..	..	..	..	..	..	..
Ether	3	2	1	..	..	..	..	..	..	..	..	..
Grand total	113	83	30	10	1	1	1	..	..	..	1	14

Stump Revision (Table 6).—Between the years 1939 and 1945, in 5 of 50 closed cases, revision was required. One of these patients died of Cl. perfringens infection. It is interesting to speculate whether or not these complications would have occurred during the antibiotic period, during which there were 33 closed cases, in none of which stump revision was required.

TECHNICAL CONSIDERATIONS

The primary consideration is the use of gentleness and minimal technical trauma on tissues which have a poor circulation and in which there may be infection in the lymphatics or blood vessels. The gangrenous and/or infected lesions which are handled so gently before operation can be severely traumatized in the operating room by unintentional rough handling of the foot and leg when they are elevated during skin preparation and draping prior to operation. This can lead to spread of infection immediately before the incision. The entire procedure should be the job of a properly indoctrinated physician and not an orderly or nurse.

Tourniquet and Refrigeration Anesthesia Contraindicated.—For approximately five years we have abandoned the use of these agents. This has been emphasized in previous communications.[4]

4. Carp, L.: Causes and Possible Reduction of Operative Mortality in Geriatric Surgery, with an Analysis of 100 Consecutive Autopsy Records, Internat. Abstr. Surg. **87**:1-18, 1948; in Surg., Gynec. and Obst., July 1948; Mortality in Geriatric Surgery, Brit. M. J. **2**:1198-1201 (Nov) 1950; Common Problems in Geriatric Surgery, Geriatrics **6**:100-111 (March-April) 1951.

The vulnerability to thrombosis of blood vessels, already diseased, from the added trauma of the vise-like grip of a tight tourniquet is demonstrated in a series of autopsy findings (Table 4). In 6 out of 11 cases of arteriosclerotic gangrene in which operations were done with this technique, massive thrombosis or embolism was the principal cause of death. The presumptive evidence is that the tourniquet was the precipitating cause of the thrombosis. It also contributes to stump breakdown from prolonged anoxia of the tissues which ultimately will form the stump. In 7 of 40 cases, this complication was seen, all in closed stumps. Another important factor is that the tourniquet does not permit vessels to bleed easily; consequently, it may be difficult to see them for ligation. Hematomas may follow. The only justification for the use of refrigeration anesthesia preliminary to operation is lack of consent for operation in the presence of ascending infection. Its spread might thus be limited.

There are authors [5] who recommend refrigeration anesthesia with tourniquet because minimal shock follows its use and because spread of infection becomes limited. This may be true in many cases, but the same result can be accomplished by early operation, by adequate preoperative preparation to include especially the maintenance of blood volume and chemical balance, and by proper choice of anesthetic, skillfully administered. Some of the above authors [6] note that wounds heal slowly and that infection frequently supervenes. Experimental studies in dogs [7] showed that prolonged refrigeration of an extremity [8] (1) delayed wound healing; (2) decreased the resistance of tissues to bacterial invasion; (3) increased wound infection in those wounds treated by delayed primary closure, and (4) predisposed to nerve degeneration. Gordon [5f] reported on six supracondylar amputations for arteriosclerotic gangrene. "We have not seen a thrombosis or embolus, delayed healing or other evidences of vascular injury in our small series." He then goes on to state that "wound healing is delayed—so that earlier removal of sutures may result in gaping of the edges." Five patients died of related causes within two months and the sixth in about one year. The causes of death are given, but there is no indication whether any were ascertained by autopsy to prove that thrombosis or embolism was not the principal cause of death. Kirz [8a] had a case of gas gangrene following refrigeration anesthesia, and he warns against the use of this method. Hughes [5d] had a related mortality of 50% in 25 cases, and there was 1 case of gas gangrene. West and Papper [9] came to the conclusion that results are

5. (*a*) Crossman, L. W.; Ruggiero, W. F.; Hurley, V., and Allen, F. M.: Reduced Temperatures in Surgery: Amputations for Peripheral Vascular Disease, Arch. Surg. **44**:139-156 (Jan.) 1942. (*b*) Melick, D. W.: Refrigeration Anesthesia, Am. J. Surg. **70**:364-368 (Dec.) 1945. (*c*) Massie, F. M.: Refrigeration Anesthesia for Amputation, Tr. South. S. A. **57**:472-482, 1946. (*d*) Hughes, E. S. R.: Refrigeration Anaesthesia, Brit. M. J. **1**:761-764 (May) 1947. (*e*) Fite, W. P., and Mengel, C. K.: Amputation of Lower Extremities in Peripheral Vascular Disease, J. Oklahoma M. A. **40**:10-12 (Jan.) 1947. (*f*) Gordon, J. B.: Experience with Refrigeration Anesthesia: 6 Supracondylar Amputations for Arteriosclerotic Gangrene, Am. J. Surg. **76**:393-397 (Oct.) 1948. (*g*) Pratt, G. H.: Amputation for Vascular Disease with Refrigeration Anesthesia, Postgrad. Med. **6**:490-493 (Dec.) 1949. (*h*) Large, A.: Physiologic Amputation by Tourniquet and Refrigeration, Arch. Surg. **60**:683-690 (April) 1950.

6. Footnotes 5*e-h*.

7. Bruneau, J., and Heinbecker, P.: Effects of Cooling on Experimentally Infected Tissues, Ann. Surg. **120**:716-726 (Nov.) 1944. Large, A., and Heinbecker, P.: Effect of Cooling on Wound Healing, ibid. **120**:727-741 (Nov.) 1944. Large, A.: Nerve Degeneration Following Prolonged Cooling of an Extremity, ibid. **120**:742-749 (Nov.) 1944.

8. Since this article was submitted for publication, there have appeared in the literature data to support the deleterious effects of refrigeration on muscle and blood vessels—production of muscle atrophy, cell death, and thrombi in vessels. Lewis, R. B., and Moen, P. W.: Further Studies in the Pathogenesis of Cold-Induced Muscle Necrosis, Surg., Gynec. & Obst. **95**:543-551 (Nov.) 1952. Pirozynski, W. J., and Webster, D. R.: Muscle Tissue Changes in Experimental Frostbite, Ann. Surg. **136**:993-998 (Dec.) 1952.

8a. Kirz, E.: Gas Gangrene After Amputation Under Refrigeration Anesthesia: A Warning, Brit. M. J. **2**:662 (Nov.) 1944.

9. West, J. S., and Papper, E. M.: Amputation in Patients with Diabetes Mellitus, New York J. M. **49**:1415-1418 (June) 1949.

better with cyclopropane, as compared with refrigeration anesthesia. Peters and his associates [10] present a table in their article which lists the results after the use of various anesthetics by several authors. The mortality was higher with refrigeration anesthesia.

Incision.—We have preferred the simple circular skin incision without long anterior or posterior skin flaps. These can be made only by undermining the skin with additional trauma and division of blood vessels.

Amputation Knife.—Charnley [11] and McMurray [12] still recommend the long-bladed amputation knife. We have discarded it as too traumatic and inexact in its section of tissues. Its rapid sweeping movement simultaneously divides many blood vessels too quickly. The result is excess bleeding, sponging, and trauma in a hurried attempt to clamp all the bleeders at once. Use of a standard sharp incision knife is the method of choice. Slow section of the tissues is then the least traumatic and most meticulous technique, and bleeders can be quickly sighted and clamped. The femoral vessels and sciatic nerve are isolated with ease.

Interdiction of Skin Clips and Clamps.—The use of towel clips which penetrate the skin is contraindicated. Such trauma may be enough to produce localized necrosis of the skin. For the same reason, the application of Allis clamps to the skin for better exposure or traction should be avoided.

Hemostasis.—The basic principle of hemostasis is to clamp all bleeding vessels with small pointed artery forceps, without inclusion of too much of the surrounding tissue. Meticulous hemostasis prevents a hematoma, which tends to delay healing and to create a dead space which may become infected and promote stump breakdown. These complications were found in several of the closed stumps. After the femoral vessels are ligated, they are transected distal to the ligature, without the application of a clamp. A small branch of the sciatic artery, the comes nervi ischiadici, which lies posteriorly in the sheath of the sciatic nerve, is included in a mass ligature of this nerve before it is sectioned high up. Individual preference determines the material of all ligatures. Residual oozing is controlled by hot/wet pads until the field is dry.

Transection of the Femur.—The level of section of the femur should be high enough proximal to the divided muscles to insure a good muscle pad over the end of the femur. Caution is necessary to avoid friction of the saw against the soft parts. We do not approve the use of a rongeur or file to round the edges of the femur stump. Periosteal and endosteal overgrowth can be prevented by pushing back the periosteum for about 3 cm. and by curetting away the bone marrow for a similar distance.

Stump Closure and Dressing.—Stump closure is advocated in all cases, except, as has been mentioned previously, in cases in which there is obvious ascending infection and in those in which the blood vessels show thrombosis or minimal bleeding at the time of operation. Whether one, two, or all the layers of muscle, fascia, and skin are approximated loosely or snugly also depends on the condition of the divided tissues. Individual preference determines the character of the suture material, which in all instances should have that fineness which is compatible with coaptation without strangulation. Small angle wound drains may be used, provided that they are removed within 48 hours, especially if meticulous hemostasis has been employed. A dry dressing with flats and fluffs is maintained in place with a snug, but not tight, bandage. Elevation of the stump on pillows adds to comfort and diminishes pain. Routine stump inspection every 48 hours will detect hematomas, infection, or sloughing. Our observations show that these complications occurred occasionally in closed stumps and that they might have been prevented if the inspection outlined above had been followed and steps initiated for more adequate drainage.

The advantages, then, of stump closure with primary or slightly delayed healing are a lower mortality, a better end-bearing stump, minimal pain and healing time, a better maintenance of chemical balance, less chance for secondary hemorrhage, and better morale for the patient.

---

10. Peters, M. P.; Broberg, G. R., and Light, G. A.: Anesthesia for Extremity Amputations: Statistical Review of 185 Major Amputation Cases, Am. J. Surg. **78**:220-225 (Aug.) 1949.

11. Charnley, J.: Amputations, Practitioner **160**:206-211 (March) 1948.

12. McMurray, B.: Mid-Thigh Amputation: Description of Technique, South African M. J. **23**:595-597 (July) 1949.

Skin Traction on Open Stumps.—This form of traction is used to help prevent retraction of the stump soft parts and thus promote faster healing and less likelihood of a stump in which the femur is in apposition to the skin. The skin traction is maintained by a medium-width, sterile stockinette applied with ace® bandages adherent to the stump skin for a distance of about 12 cm. The stockinette is permitted to protrude beyond the skin for a sufficient distance to allow for the stump dressing. Four layers of sterile splint cotton are rolled around the adherent stockinette. Over this, a roll of 6 in. (15 cm.) fast-setting plaster is applied. When it has set, a wire ladder splint, bent in the shape of a "U" and projecting anteroposteriorly for about 30 cm. beyond the stump, is incorporated over the plaster by another plaster roll. The apex of the stockinette is closed by means of adhesive tape, and the desired traction is maintained from the stockinette to the summit of the wire ladder by elastic tubing or by two stout rubber bands. The traction has served its purpose when the stump tissues have become set without their retraction. After that, an elastic ace® bandage from above downward helps to close dead spaces until the final healing.

NUTRITIONAL CONSIDERATIONS

Good nutrition, vitamin therapy, good chemical and fluid balance, and meticulous care of the diabetes must supplement good surgery if it is to be effective for wound healing. The type of patient under discussion is usually averse to oral food and water intake; consequently, the less effective parenteral therapy is substituted too frequently, especially when personnel is insufficient to force feed the patient. This is a continuing problem and it means painstaking organization of nurses and attendants so that patients receive their required caloric, protein, and fluid intake at regular intervals. In many instances, patients cannot help themselves. It is one thing to serve them food, but it is another to see that they eat it and thus help themselves to avoid dietary invalidism.

SUMMARY

One hundred thirteen consecutive midthigh amputations for arteriosclerotic and/or diabetic gangrene of the lower extremities between 1939 and 1952 are analyzed in 108 chronically ill patients, practically all of whom were 60 years of age and over, with special reference to operative management and its results. Five of the patients had bilateral amputations. Sixty-eight of the patients were men and 40 women. The arteriosclerotic group predominated among the former, and the diabetic group among the latter. Most of the patients were in the eighth decade.

Forty-five patients died, and the mortality rate was 40%. A predisposing cause of death was delayed operation from so-called conservatism or from lack of consent for operation. The principal causes of death were bronchopneumonia, cardiac failure, and thrombosis and embolism. Other causes of death were hemorrhage from the femoral artery in an open stump, shock, and heat exhaustion. Seventeen autopsies were performed. The mortality rate among patients who had open stumps with traction was 50%. By comparison, it was 37% in those who had closed stumps.

Refrigeration anesthesia with tourniquet is contraindicated as a routine measure because the mortality rate is 50%, as compared with 33% among patients who had other anesthetic agents. Morbidity is also increased from stump breakdown. The thermal and tourniquet trauma predispose to tissue anoxia and thrombosis in major blood vessels, as demonstrated in 6 out of 11 autopsies on patients who had midthigh amputations for arteriosclerotic gangrene.

During the chemotherapeutic period (1939 to 1945), the average closed stump healing time for arteriosclerotic patients was 20 days and for diabetic patients

30 days. In the subsequent antibiotic period (1946 to 1952), the average healing time was shortened to about 10 days for each group. In this same period, it took approximately five times as long for the healing of open stumps with traction. Because of the shorter healing time with corresponding lower morbidity and mortality, closed stumps are preferable to open stumps, except in patients with obvious ascending infection or thrombosis of the femoral vessels. Since open stumps were preferred in the latter cases, a comparison of the mortality in the arteriosclerotic and diabetic groups is not wholly conclusive for the respective merits of the open and closed stump methods. However, since the group comprising the 15 open stumps in each group turns out to be a true sample as far as ages are concerned, a comparison of the mortality in the arteriosclerotic and diabetic groups is statistically consistent. The mortality for the closed and open stump cases showed no consistent difference for the arteriosclerotic cases. It was about 45%. On the other hand, the mortality for diabetics was 24% for closed stumps, as compared with 53% of mostly routine open stumps. This result points to the preference for closed stumps in diabetic patients.

Suggestions are made for operative technique which will produce the least amount of trauma to tissue which already has severe circulatory deficiency. The importance of meticulous hemostasis is stressed. Inspection of closed stumps is recommended within 48 hours to ascertain whether there is need for drainage.

Nutritional requirements and supportive therapy for the patient are emphasized.

CORRECTION

In the article by Captain Simpson, "Foreign Body of Embolic Origin in Right Ventricle of Heart Removed with Successful Result," printed in the December issue, page 926, the following changes should be made: The last sentence of the first paragraph should read: "A drainage site of about 2 cm. would fulfill the requirements of safety and insure adequacy of drainage." On page 929 the legend to Figure 4 should read: Fig. 4.—Photomicrograph of metallic foreign body removed, showing adherent cloth (United States Army Signal Corps photograph).

Case Reports

STUDIES IN STRANGULATION OBSTRUCTION

III. Recovery of an Abnormal Hemin Pigment in the Human

ISIDORE COHN Jr., M.D., M.Sc. (Med.)
HERBERT R. HAWTHORNE, M.D.
PAUL NEMIR, M.D.
AND
DAVID L. DRABKIN, M.D.
PHILADELPHIA

IN AN EXPERIMENTAL study of strangulation obstruction, we found a previously undescribed and, as yet, unidentified pigment in the peritoneal fluid.[1] This has stimulated a search for the pigment in clinical cases of comparable nature, and for the two years of our study, seven of the largest hospitals in Philadelphia have been attempting to supply us with peritoneal fluid from all patients operated on for intestinal obstruction with suspected strangulation.[2] Two personally observed cases of mesenteric arterial thrombosis requiring resection of all but 16 and 32 cm. of small bowel failed to show any significant spectrophotometric changes in the peritoneal fluid. Thus the demonstration of this pigment in a case with compromised blood supply to the small bowel seemed of sufficient interest to warrant a brief report of its occurrence. Since there are many reasons to indicate that the interference with the blood supply in the obstruction experiments is essential to the production of the pigment, and since the compromised blood supply in the case here reported simulates that portion of the problem, it is felt that the demonstration of the pigment in this clinical case is in every way comparable to its appearance in the experimental animals.

REPORT OF A CASE

S. S., a 62-year-old white man, was admitted to Graduate Hospital, on the service of Dr. H. L. Bockus, on Oct. 21, 1950. A diagnosis of duodenal ulcer had been repeatedly confirmed by x-ray studies. Even though cardiovascular studies revealed severe myocardial disease, surgery

Dr. Cohn's present address: Department of Surgery, Louisiana State University School of Medicine, New Orleans.

From the Departments of Surgery and Physiological Chemistry, Graduate School of Medicine, University of Pennsylvania, Philadelphia.

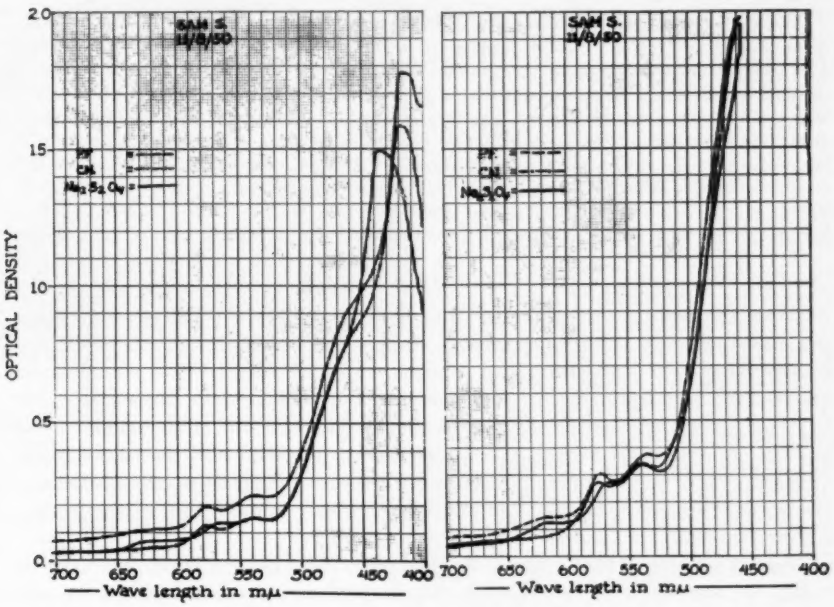
Abstract of a portion of a thesis submitted by Dr. Cohn in partial fulfillment of the requirements for the degree of Master of Medical Science for graduate work in Surgery at the Graduate School of Medicine, University of Pennsylvania.

1. Nemir, P. Jr.; Hawthorne, H. R.; Cohn, I., Jr., and Drabkin, D. L.: The Cause of Death in Strangulation Obstruction: An Experimental Study. I. Clinical Course, Chemical, Bacteriologic and Spectrophotometric Studies, Ann. Surg. **130**:857, 1949; II. Lethal Action of the Peritoneal Fluid, ibid. **130**:874, 1949.

2. Cohn, I., Jr.: The Correlation of the Bacteriology and Spectrophotometry of the Peritoneal Fluid with the Clinical Picture in Strangulation Obstruction, Thesis, Graduate School of Medicine, University of Pennsylvania, 1952.

was advised because of previous failures of medical management. On Nov. 1, 1950, an uneventful subtotal antecolic Hoffmeister gastrectomy was performed (I. C., Jr.).

Postoperative Course.—On the first day, the patient was ambulatory. The parenteral intake was 2,060 cc., and the renal output 1,200 cc. The second day was uneventful. The temperature remained below 99 F. He took 30 cc. of water or tea hourly all day. On the third day he was ambulatory and taking fluid by mouth. By 6 p. m. the urinary output was 250 cc., while the intake was 2,800 cc. Slight abdominal distention was relieved by an enema. At 9 p. m. he was pale, sweating, and apprehensive, but did not complain of any pain, dyspnea, nausea, or substernal distress. The systolic pressure was 48 to 60. The diastolic pressure was not obtained. The electrocardiogram was unchanged. Twenty to 40 cc. of hemolyzed blood were aspirated from the stomach. Impressions were (1) silent coronary thrombosis; (2) intragastric hemorrhage and shock; (3) pulmonary embolism, and (4) catastrophic intra-abdominal accident, possibly



Spectrophotometric curves from the peritoneal fluid obtained at death. Both curves are from same fluid but have been obtained by readings at different dilutions. Significant changes in $Na_2S_2O_4$ curve in 565 to 530 mμ region are visible in both graphs. Maximum in plain peritoneal fluid at 450 mμ is visible only in Chart on left.

mesenteric thrombosis or volvulus. Coronary occlusion was excluded and shock therapy begun. By midnight the acute shock phase had ended; the temperature had risen to 100 F., and pain and guarding were noted in the left upper quadrant. An anastomotic leak or hemorrhage were considered, but the patient's condition was too precarious to justify reexploration. On the fourth day the temperature was 104.2 F., rectally; pulse rate, 140, and respiration, 24. Peritonitis from a leaking anastomosis seemed certain. The abdomen was silent, and distention had increased. A flat plate revealed gaseous distention, but no free air was present under the diaphragm. The fifth day the temperature dropped to normal, but the patient was oliguric. The presence of blood in the gastric suction confused the diagnosis, but it was decided to continue treatment for peritonitis. On the sixth day, jaundice appeared. The temperature rose gradually to 103.4 F. The urinary output during the terminal 24 hours was 30 cc. The patient died on the seventh postoperative day, 81 hours after the onset of the acute episode.

Autopsy.—Permission was granted for only a limited autopsy through the operative incision.[3] The peritoneal cavity contained 300 to 400 cc. of a dark, reddish-brown, serosanguineous fluid. There was no evidence of bacterial peritonitis. All suture lines were intact and watertight. From the gastric stump to within 2 or 3 ft. (60 to 90 cm.) of the ileocecal valve the bowel was markedly and uniformly cyanotic. The spleen and liver showed increased friability. One of the major branches of the superior mesenteric artery was opened and traced as far back to the parent vessel as possible. Neither clot nor fluid blood was found in the lumen of the vessel, and it was concluded that the thrombus had occluded both the superior mesenteric artery and the celiac axis. Time limitations set by the family did not permit further exploration of either of these vessels.

Pathologic Report on Liver and Spleen.—"Liver shows at least one small fresh infarct, a fact which points strongly to severe sudden ischemia. Examination of the spleen is inconclusive. Diagnosis is infarct of liver." This report tends to support the diagnosis of mesenteric and celiac axis thrombosis.

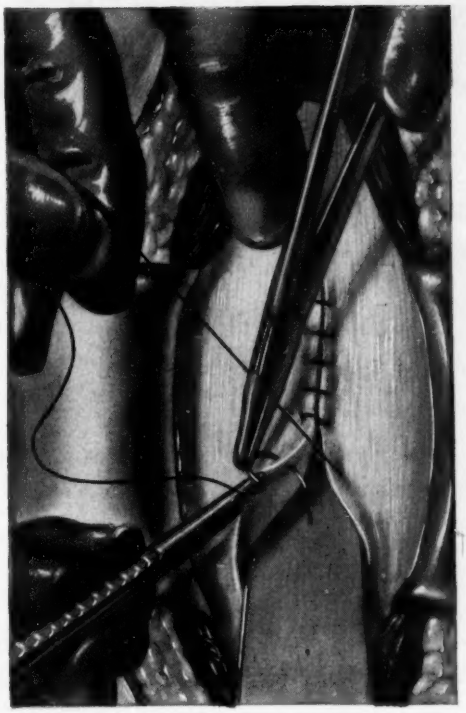
Spectrophotometric Examination of the Peritoneal Fluid (Chart).—This examination, by one of us, showed the "typical" changed pigment previously reported in the peritoneal fluid of dogs with strangulation obstruction. In the curve for deoxygenated hemoglobin, obtained after treating the fluid with $Na_2S_2O_4$, there are two maxima in the green region (565 to 530 mμ), in contrast with the one maximum usually seen, and thus indicating an irreversible change in the hemoglobin. In the curve for the plain peritoneal fluid, there is the suggestion of the presence of bile pigment in the maximum at 450 mμ. There is also the usual indication of the presence of methemoglobin, which has been uniformly present to some extent in the experimental, as well as in all other, clinical cases.[4] These changes are the same as those previously reported in experimental work and indicate that the pigment found there can also be formed in the human.

COMMENT

Since the abnormal curves were obtained in the peritoneal fluid, bowel contents, and blood of dogs with experimental strangulation obstruction, we have been attempting to find such changes in humans who have likewise had strangulation obstruction. Our search to this point has been unrewarding. We are aware of the fact that this patient had no obstruction, but he did have the strangulation in the form of an arterial thrombus, and he also had an ileus. We feel that the vascular impairment is of prime importance in the formation of the pigment and was present, though in different form, both in the experimental animals and in the patient reported on here.

We are not prepared to evaluate the final significance of these spectrophotometric changes at this time. We do not claim that the pigment responsible for the spectrophotometric changes is the lethal agent which caused the death either of this patient or of the experimental animals in which it was found. In the experimental animals it was found as an accompaniment to the strangulation obstruction. While the pigment has not been definitely identified, similar irreversible alterations of the hemoglobin pigment have been obtained in vitro, and this work is being subsequently reported. The pigment change may serve as the only detectable manifestation of a general change in protein structure and may be useful as an indicator. We report it at present because it is the first time, to our knowledge, that this pigment has been found in the human and because of our interest in the fact that it was found in a patient with vascular complications similar to those of strangulation obstruction. We also report it because we feel that since it has been found in the human, as well as in the experimental animal, it should stimulate a further search for its true nature and its correlation with the lethal agent in strangulation obstruction.

3. Autopsy was performed by Dr. D. L. Moore, resident in surgery.
4. Nemir.[1] Cohn.[2]



Wounds sutured with smaller sizes of D & G surgical gut on Atraumatic needles have less trauma and heal faster and more evenly.

faster wound healing

Patients move about more freely after their operations and are out of the hospital sooner when their wounds have been closed with a minimum of trauma. Davis & Geck offers two modern aids to faster and more even healing:

1. Davis & Geck "timed-absorption" surgical gut—in small sizes
2. Davis & Geck Atraumatic® needles

faster healing with smaller sizes of surgical gut

Davis & Geck surgical gut sutures may be used in smaller sizes than might be expected because *diameter for diameter* the tensile strength is unexcelled by any other brand. By a unique process of control, these "timed-absorption" sutures offer maximum resistance to digestion during the early days when the wound is weakest. After healing is under way, digestion is more rapid until completed. Smaller suture sizes permit closer approximation and provoke less trauma. The patient's convalescence is smoother.

faster healing with Atraumatic® needles

In suturing with Atraumatic needles there is less tissue trauma, faster and more even healing. The D & G Atraumatic needle is joined to its suture smoothly. Needle and suture are about the same diameter. No big eye and double strand of suture are dragged through the tissue. Sutures on Atraumatic needles are economical, too. Surgery is easier and faster, needles are always sharp, *no time is lost while the nurse threads needles.*

For better wound healing, use the smaller sizes of Davis & Geck "timed-absorption" sutures, with an Atraumatic needle attached, on your next wound closure.

Davis & Geck, Inc.

A UNIT OF AMERICAN Cyanamid COMPANY

57 Willoughby Street, Brooklyn 1, N.Y.

The IONIC BONE DECALCIFIER

Decalcifies blocks of bone -Quickly and safely **With little attention**
No electrical adjustments **No overheating**

Specimens processed
Undistorted
In pyrex cup
Minimum handling
No danger of loss
Stain beautifully

The IONIC BONE DECALCIFIER, with four decalcifying cells, (two are extra)

Supplied complete Ready to operate Platinum included Electrodes formed
Can handle FOUR separate specimens simultaneously with ease

IONIC BONE DECALCIFIER, Model DC-5, complete with two decalcifying cells and platinum, instructions, without acids, $139.70

Extra Decalcifying Cells, complete, each, $34.50
Larger Decalcifying Cells available

Write for details

The MARTIN SWEETS Company

126 SOUTH FIRST STREET
LOUISVILLE 2, KENTUCKY

Close-up of Eye Taken with New Exakta "VX" Camera

New Model With Pre-Set Diaphragm Control

EXAKTA "VX"

35 mm Single-Lens Reflex Camera For Parallax-Free Surgical Photography

The Exakta, with instantly interchangeable lenses, is widely used in hospitals for operation room photography. Its unique through-the-lens viewing system assures absolutely correct "on-the-subject" photographs during every step of the operation. In addition, this world famous medical camera is regularly used for preliminary, developmental, and end result pictures of patients; for copying X-Rays; and for making color transparencies of injuries and lesions—a necessity for recording and lecturing.

With f2.8 Zeiss Tessar "T" Coated Lens with Pre-Set Diaphragm	**$269.50**
Penta-Prism Eye Level Reflex Viewfinder	**50.00**
Extension Tube Set	**24.00**
Microscope Adapter	**29.50**

Write Dept. 800 for free descriptive booklet "H" on camera and accessories and brochure on close-up technique with the Exakta.

EXAKTA CAMERA CO., 46 W. 29th St., N. Y. 1, N. Y.

Exclusive Sales and Service Organization in the U.S.A. for Ihagee Camera Works, Germany

---

BOOKLETS ON MENTAL HYGIENE

Here are several booklets on mental hygiene that may prove of interest and use to you and your patients.

EMOTIONAL HEALTH IN WORK AND PLAY. T. R. Retlaw. 8 pages. 15 cents.

MEETING EMOTIONAL DEPRESSION. Franz Alexander. 16 pages. 15 cents.

REPORT OF A.M.A. COMMITTEE ON MENTAL HEALTH. 48 pages. 15 cents.

MESMERISM MINUS MESMER. Stefan Zweig. A discussion of hypnotism. 5 pages. 5 cents.

NERVOUSNESS. Isidore Margaretten. 4 pages. 5 cents.

THE TYRANNY OF NERVES. Eoline Church Dubois. 3 pages. 5 cents.

SHOCK THERAPY SAVES MINDS. Harold Shryock. 5 pages. 5 cents.

Keep a supply of these booklets on hand. Available at lower cost for quantity purchases.

AMERICAN MEDICAL ASSOCIATION
535 North Dearborn Street
Chicago 10, Illinois

BARD ◇ U.S.C.I. Woven Catheters

The Smaller Sizes
are COLOR-BANDED
for Easy Selection
Reg. U.S. Pat. Off. 535061

"The Accepted Standard of Excellence"

BARD ◇ U.S.C.I. WOVEN CATHETERS

are precision engineered of fine materials for dependable service. They possess the proper degree of flexibility for facile introduction. The eyes and lumen are uniformly of the correct size for adequate drainage. They are sterilizable by boiling or autoclaving. For cold sterilization we recommend Detergicide.

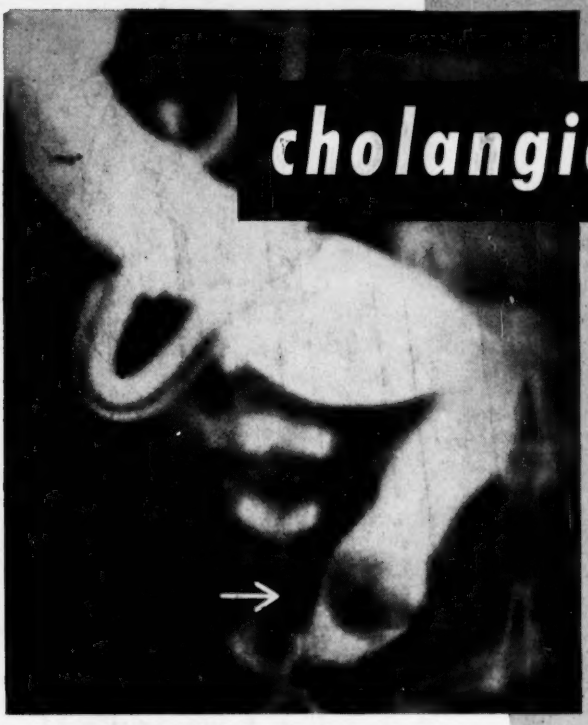
See Your Surgical Supply Dealer

When a human life may be at stake there can be no Compromise with ***Quality***

BARD UROLOGICAL INSTRUMENTS

C. R. BARD, Inc., Summit, N. J.
Distributors for
UNITED STATES CATHETER and INSTRUMENT CORP.

THERE IS NO SATISFACTORY SUBSTITUTE FOR QUALITY



cholangiography

Cholangiogram with Diodrast 35% showing stone in distal end of common duct. Illustration, courtesy of Dr. J. Buckstein, author of "The Digestive Tract in Roentgenology" (Lippincott, 1948) in which a whole chapter is devoted to this procedure.

Easy Roentgenologic Detection of "the 10 to 18 per cent of stones left behind after common duct exploration" [1]

"Since 1934 we have employed visualizing cholangiograms in all operations on the extrahepatic biliary system. More than 1700 studies have been made and from this experience much information has been obtained. Operative cholangiograms demonstrate congenital aberrations and anatomic displacements of the extrahepatic biliary system; determine patency of the ductal system; note number and position of offending calculi; designate functional status of the sphincter of Oddi; outline fistulous communications; visualize bile reflux into the pancreatic ducts; detect intrusions of neoplasms which impinge on the large bile ducts or originate in the ampulla of Vater; and visualize dilatation, sacculation or diverticular enlargements of the bile ducts themselves. Such exact information permits the surgeon to select the operative procedures best suited to alleviate existing pathologic abnormalities." [2]

1. Byrne, R. V.: *Amer. Jour. Surg.*, 78:514, Oct., 1949.
2. Hicken, N. F., Stevenson, U. L., Franz, B.J., Crowder, Earl: *Amer. Jour. Surg.*, 78:347, Sept., 1949.

Diodrast®

35% SOLUTION

BRAND OF IODOPYRACET INJECTION

For Clear Visualization of the Biliary Tract

Also Urinary Tract, Arteries, Veins

Ampuls of 10, 20 and 30 cc.

Simplified Technic

For a detailed discussion of a simple fractional method for cholangiography postoperatively or operatively write for illustrated pamphlet.

Winthrop-Stearns INC.

NEW YORK 18, N. Y. WINDSOR, ONT.

Diodrast, trademark reg. U. S. & Canada